FDA Briefing Document

Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee

April 24 and 25, 2018
The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought supplemental new drug application (sNDA) 020998/S-050, Celebrex (celecoxib) capsules, submitted by Pfizer, Inc., to this Advisory Committee in order to gain the Committee’s insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee

April 24-25, 2018

Briefing Materials

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DATE: March 27, 2018

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

RE: Overview of the April 24-25, 2018 Joint meeting of FDA’s Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee

Following emergence of new data about the risk of cardiovascular (CV) thromboembolic events associated with the cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs), rofecoxib and celecoxib, a joint advisory committee meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held in February 2005. During the 2005 meeting, data from clinical outcome trials and epidemiology studies of several individual NSAIDs were reviewed, and the committee discussed the risk of CV thromboembolic events associated with the use of both COX-2 selective and nonselective NSAIDs. Based on the data reviewed and the deliberations of the advisory committee members, FDA concluded that the risk for CV thromboembolic events was present for both COX-2 selective NSAIDs and nonselective NSAIDs, and the data available at the time did not permit rank ordering of the drugs regarding CV risk.1

In 2006, a large randomized controlled trial (RCT) intended to evaluate cardiovascular (CV) thrombotic risk called “Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen” (PRECISION) was initiated after Pfizer agreed to conduct a postmarketing commitment to evaluate the CV thrombotic risk of celecoxib requested by the Agency. It was a randomized, double-blind, active-controlled, parallel-group study of CV safety in osteoarthritis or rheumatoid arthritis patients with or at high risk for CV disease comparing celecoxib with naproxen and

ibuprofen. The trial had originally been anticipated to be completed by December 2013; however, event accrual occurred more slowly than anticipated.

While the PRECISION trial was under way, numerous epidemiological studies and meta-analyses of RCTs were conducted examining the relationship between NSAID use and CV thrombotic risk, including identifying risk factors for the adverse event. In February 2014, a joint meeting of the Arthritis Advisory Committee (AAC) and Drug Safety and Risk Management Advisory Committee (DSaRMAC) discussed data from the epidemiological studies and meta-analyses of RCTs examining the risk of cardiovascular (CV) thromboembolic events associated with the use of NSAIDs published after the February 2005 joint advisory committee meeting.

Following internal Agency discussion and consideration of the 2014 AC discussion, as well the revision of a class labeling template for the NSAIDs, a Safety Labeling Change was required for the NSAID class in July 2015 to incorporate the information drawn from the published epidemiological studies and meta-analyses, and the AC discussion.

The highlights of the labeling changes related to CV thrombotic risk required for the NSAID class follow below:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for FDA to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

The labeling required in the Safety Labeling Change notification letter was approved in May 2016 for the entire NSAID class.

The results of the PRECISION trial were published in the New England Journal of Medicine in November 2016, and the full clinical study report of the trial was submitted to FDA in June 2017. The primary aim of the PRECISION trial was to assess the CV risk
of celecoxib compared to naproxen and ibuprofen in a population of osteoarthritis and rheumatoid arthritis patients with CV disease (CVD) or risk factors for CVD. The primary Antiplatelet Trialists’ Collaboration (APTC) endpoint of PRECISION was an independently adjudicated composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke. The primary hypothesis tested in PRECISION was that celecoxib was non-inferior to naproxen for the APTC endpoint. Hypotheses also tested were whether celecoxib was non-inferior to ibuprofen, and whether ibuprofen was non-inferior to naproxen for the APTC endpoint.

With the focus on a patient population enriched for CVD, about 45% of the study population were taking cardioprotective doses of aspirin. Because ibuprofen and naproxen both act as reversible inhibitors of cyclooxygenase-1 (COX-1), they can interfere with aspirin’s antiplatelet activity (due to irreversible inhibition of COX-1). The NSAID interactions with aspirin had potential clinical implications on the occurrence of the primary study outcome of the APTC composite CV endpoint (non-fatal myocardial infarction [MI], non-fatal stroke, CV Death). Drug interaction studies conducted for each of the studied NSAIDs with aspirin will be reviewed as part of the AC meeting, so that these interactions can be considered during the interpretation of the trial results.

The Committees will be asked to consider the following discussion topics on April 24-25, 2018:

**PRECISION trial**
1. Discuss evidence from the PRECISION trial that supports cardiovascular safety for celecoxib.
2. Discuss limitations of the PRECISION trial including, but not limited to, the comparability of the dosing regimens that may interfere with interpretability of the cardiovascular outcome results.
3. Has the PRECISION trial demonstrated cardiovascular safety for celecoxib comparable to naproxen and ibuprofen?
4. Discuss how you interpret the secondary and tertiary endpoints of the trial given how they were clinically defined and that there was not a pre-specified hierarchical statistical testing plan.

**Aspirin-NSAID interaction**
1. Discuss whether there is a clinically significant interaction between aspirin and celecoxib? Aspirin and ibuprofen? Aspirin and naproxen?
2. Is there a patient population (e.g., patients with recent MI, revascularization, stent placement) for whom the risks of an aspirin-NSAID interaction outweigh the benefits of the NSAID?
3. Based on the available data, does the interaction between aspirin and each the NSAIDs studied warrant a contraindication for vulnerable populations (e.g., patients with recent MI, revascularization, stent placement)?
4. For over-the-counter (OTC) naproxen and ibuprofen products, the committees will be asked to discuss:
a. Whether the Drug Facts label should warn that naproxen may decrease the cardiovascular event prevention benefit of aspirin

b. Whether consumers who take aspirin for cardiovascular event prevention should not concomitantly take naproxen

c. Whether consumers who take aspirin for cardiovascular event prevention should not concomitantly take ibuprofen
## Integrated Summary Memorandum

**Joint meeting of FDA’s Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee – April 24-15, 2018**

Division of Anesthesia, Analgesia, and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Celebrex (celecoxib)</th>
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<tbody>
<tr>
<td>NDA#</td>
<td>20998, supplement 050</td>
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<tr>
<td>Safety Issue Name</td>
<td>Cardiovascular thrombotic risk</td>
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<td>PRECISION review team</td>
<td>Division of Anesthesia, Analgesia, and Addiction Products</td>
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<td>Drs. Pokrovichka, Lloyd, Racoosin, Darkwah</td>
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<td>Division of Cardiorenal Products</td>
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<td>Dr. Hariharan</td>
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<td>Drs. N. Pratt, Falconer, Mistry, Mathew, Chai</td>
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<td>Office of Scientific Investigation</td>
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<td>Drs. Green, Kronstein</td>
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1 Background information on the NSAID class
1.1 General information
Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs used to treat inflammation, pain, and fever. Table 1 below presents the various NSAID classes and drugs within each class that are currently available in the United States. Among these, aspirin, magnesium salicylate, choline salicylate, sodium salicylate, ibuprofen, and naproxen are available for nonprescription (over-the-counter or OTC) use.

Table: NSAID Classes and Drugs That are Currently Available in the United States
*Active ingredients found in oral nonprescription drugs are marked by an asterisk.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
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<tbody>
<tr>
<td>Salicylates</td>
<td>Aspirin (acetylated salicylate)*</td>
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<tr>
<td></td>
<td>Buffered aspirin*</td>
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<tr>
<td></td>
<td>Carbaspirin calcium*</td>
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<tr>
<td></td>
<td>Magnesium salicylate*</td>
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<td>Choline salicylate*</td>
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<td>Sodium salicylate*</td>
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<tr>
<td></td>
<td>Diflunisal</td>
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<tr>
<td>Propionic acid derivatives</td>
<td>Ibuprofen</td>
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<tr>
<td></td>
<td>Naproxen*</td>
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<td></td>
<td>Ketoprofen</td>
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<td>Flurbiprofen</td>
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<td></td>
<td>Enoprofen</td>
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<td></td>
<td>Oxaprozin</td>
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<tr>
<td>Acetic acid derivatives</td>
<td>Ketorolac</td>
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<td></td>
<td>Indomethacin</td>
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<td></td>
<td>Tolmetin</td>
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<td></td>
<td>Nabumetone</td>
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<td>Sulindac</td>
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<td></td>
<td>Etodolac</td>
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<tr>
<td></td>
<td>Diclofenac</td>
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<tr>
<td>Enolic acid derivatives</td>
<td>Piroxicam</td>
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<td></td>
<td>Meloxicam</td>
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<tr>
<td>Fenamic acid derivatives</td>
<td>Meclofenamate</td>
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<tr>
<td></td>
<td>Mefenamic acid</td>
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<tr>
<td>Diaryl heterocyclic NSAIDs (COX-2 selective)</td>
<td>Celecoxib</td>
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The mechanism of action of NSAIDs is the inhibition of prostaglandin synthesis.\(^1\) Prostaglandins are involved in inflammation, pain, fever, and blood clotting. NSAIDs suppress the production of prostaglandins by inhibiting enzymes needed for prostaglandin biosynthesis called cyclooxygenases (COX). The COX enzymes play a key role in the production of prostaglandins by converting arachidonic acid to prostaglandin H\(_2\) (PGH\(_2\)), which is metabolized by specific isomerases to tissue-specific prostanoids – prostacyclin (PGI\(_2\)), thromboxane (TXA\(_2\)), prostaglandin D\(_2\) (PGD\(_2\)), prostaglandin E\(_2\) (PGE\(_2\)), and prostaglandin F\(_2\) (PGF\(_2\)) [Figure 1]. NSAIDs inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) to varying degrees.\(^2\), \(^3\), \(^4\) Inhibition of COX-1 by NSAIDs prevents the formation of thromboxane from the arachidonic acid derivative prostaglandin H\(_2\), and thereby prevents thromboxane-induced platelet aggregation. The inhibition of COX-2 is thought to mediate the antipyretic, analgesic, and anti-inflammatory actions of NSAIDs.\(^5\) Most NSAIDs are competitive, reversible inhibitors of the COX enzymes. However, aspirin acetylates the isoenzymes and inhibits them irreversibly.

**Figure 1: The Cyclooxygenase Pathway**

\[\text{Arachidonic acid} \overset{\text{NSAID}}{\longrightarrow} \text{COX-1} \longrightarrow \text{COX-2 inhibitor} \overset{\text{NSAID}}{\longrightarrow} \text{PGH}_2 \]

- PG\(_I_2\): Endothelium, kidney, platelets, brain
- TXA\(_2\): Platelets, vascular, smooth-muscle cells, macrophages, kidney
- PGD\(_2\): Mast cells, brain, airways
- PGE\(_2\): Brain, kidney, vascular smooth-muscle cells, platelets
- PGF\(_2\): Uterus, airways, vascular smooth-muscle cells, eye

Source: Profit and Chrisp 2007

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1.2 Drug Utilization

An estimated 70 million prescriptions were dispensed from U.S. retail pharmacies for celecoxib, ibuprofen, or naproxen single ingredient products in 2017. Of these prescriptions, ibuprofen single ingredient products accounted for the largest proportion of use at 64% (44.8 million prescriptions), followed by naproxen single ingredient products at 26% (18 million prescriptions) and celecoxib at 10% (7.3 million prescriptions) of total prescriptions. Prescription utilization appeared to increase for ibuprofen and naproxen single ingredient products from 2006 through 2017; meanwhile, utilization of celecoxib decreased over the last twelve years. Further details are provided in Section 8, Drug Utilization Summary.
2 Regulatory History

2.1 NSAID-associated cardiovascular thrombotic risk

2.1.1 2005 Advisory Committee meeting and labeling change

Over the early part of the 2000s, data began to emerge from large randomized controlled clinical trials demonstrating cardiovascular thromboembolic risk with the COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs), a subgroup of the broader class of NSAIDs. In September of 2004, the voluntary withdrawal of rofecoxib by Merck Pharmaceuticals following identification of an elevated risk for cardiovascular events in a clinical trial of familial adenomatous polyposis (Adenomatous Polyp Prevention on Vioxx [APPROVe]) created an opportunity for a review of the available clinical trial data and epidemiologic studies for all the COX-2 selective and non-selective NSAIDs. Studies reviewed included efficacy trials in rheumatologic conditions, outcome studies with prespecified gastrointestinal and cardiovascular (CV) safety endpoints, and other trials in conditions where inflammation was postulated to have an etiological effect, including familial polyposis and Alzheimer’s disease. On February 16-18, 2005, a joint meeting of FDA’s Arthritis Advisory Committee and FDA’s Drug Safety and Risk Management Advisory Committee was convened to discuss the risk of cardiovascular thromboembolic events with COX-2 selective NSAIDs and non-selective NSAIDs (e.g., ibuprofen, naproxen, diclofenac, and others).

At the meeting, the advisory committee opined that there appeared to be a class effect for cardiovascular risk associated with the three approved COX-2 selective NSAIDs (i.e., rofecoxib, celecoxib, and parecoxib/valdecoxib); there was less agreement with regard to the non-selective NSAIDs, but the general recommendation was that similar warnings be applied to these drug labels as well.

Following the advisory committee meeting, on April 7, 2005, the FDA made the following conclusions:

- The three approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with an increased risk of serious adverse CV events compared to placebo. The available data do not permit a rank ordering of these drugs regarding CV risk.

- Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.

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6 See Appendix 1 for a table summarizing the large randomized controlled trials in which celecoxib was studied.

• Long-term placebo-controlled clinical trial data are not available to adequately assess the potential for the non-selective NSAIDs to increase the risk of serious adverse CV events.

• Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.

• Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately post-operative from coronary artery bypass (CABG) surgery).

• Valdecoxib is associated with an increased rate of serious and potentially life-threatening skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other COX-2 selective agents and is the only NSAID with a boxed warning for this adverse event in its approved package insert. In the absence of any demonstrated advantage over nonselective NSAIDs, the overall benefit versus risk profile for valdecoxib is unfavorable for marketing.

Based on these conclusions, FDA took the following actions:

• The agency asked Pfizer to voluntarily withdraw Bextra (valdecoxib) from the U.S. market.

• The professional labeling for all prescription NSAIDs was revised to include a boxed warning highlighting the potential increased risk of serious adverse CV events. The boxed warning also includes the well described NSAID class risk of serious, and often life-threatening, GI bleeding, which is currently contained in a bolded warning.

• The labeling for all prescription NSAIDs was revised to include a contraindication for use in patients immediately post-operative from CABG surgery.

• A class NSAID Medication Guide was developed and implemented to inform patients of the potential increased risk of serious adverse CV events and the risk of serious GI bleeding.

• The labeling for non-prescription NSAIDs was revised to include more specific information about potential CV and GI risks and information to assist consumers in the safe use of these drugs.

• The agency requested that all sponsors of non-selective NSAIDs conduct and submit for FDA review a comprehensive review and analysis of available controlled clinical trial databases to further evaluate the potential for increased CV risk.

For additional details of the regulatory history and discussions leading to these conclusions and actions, the reader is referred to the Decisional Memorandum dated April 6, 2005 (authored by
Dr. John Jenkins formerly of the Office of New Drugs (OND) and Dr. Paul Seligman formerly of the Office of Pharmacoepidemiology and Statistical Science) which is included in this background package and also available at this link: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106201.pdf

Around this same time, the European Medicines Agency (EMA) took action on COX-2 selective NSAIDs and non-selective NSAIDs. The EMA came to a different conclusion than FDA and distinguished COX-2 selective NSAIDs as having increased CV thrombotic risk compared to non-selective NSAIDs. EMA made the following recommendations/conclusions:

• COX-2 selective NSAIDs
  – Addition of contraindications stating that COX-2 selective NSAIDs must not be used in patients with established ischemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease
  – Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 selective NSAIDs to patients with risk factors for heart disease, such as hypertension, hyperlipidemia, diabetes, and smoking
  – Given the association between cardiovascular risk and exposure to COX-2 selective NSAIDs, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment

• Non-selective NSAIDs
  – Non-selective NSAIDs are important treatments for arthritis and other painful conditions.
  – It cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events especially when used at high doses for long-term treatment.
  – The overall benefit-risk balance for non-selective NSAIDs remains favorable when used in accordance with the product information, namely on the basis of the overall safety profile of the respective non-selective NSAID, and taking into account the patient’s individual risk factors (e.g. gastrointestinal, cardiovascular and renal).
Following announcement of the April 7, 2005 action, a letter was issued on June 14, 2005, to all NSAID sponsors requesting that a boxed warning be added to labeling describing the cardiovascular and gastrointestinal risks along with related changes to other sections of labeling. The letter also requested the addition of a Medication Guide that would be distributed with each dispensed prescription to explain these risks in patient friendly language. The updated labeling was implemented in the next several months following the labeling supplement request. The boxed warning and warning statement are shown below:

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS and CLINICAL TRIALS).

- TRADENAME is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See WARNINGS).

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see WARNINGS, GI Effects).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

The sponsors of the non-selective NSAIDs submitted their reviews of all clinical trial data available to them to evaluate the potential for cardiovascular risk of each of the NSAIDs. The data in these submissions were limited and did not result in new insights about the cardiovascular risks of the non-selective NSAIDs.
In 2006, a large randomized controlled trial (RCT) intended to evaluate cardiovascular (CV) thrombotic risk called “Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen” (PRECISION) was initiated after Pfizer agreed to conduct a postmarketing commitment to evaluate the CV thrombotic risk of celecoxib requested by the Agency.\(^8\) It was a randomized, double-blind, active-controlled, parallel-group study of CV safety in osteoarthritis or rheumatoid arthritis patients with or at high risk for CV disease comparing celecoxib with naproxen and ibuprofen. PRECISION’s primary Antiplatelet Trialists’ Collaboration (APTC) endpoint was an independently adjudicated composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke. The primary hypothesis tested in PRECISION was that celecoxib was non-inferior to naproxen for the APTC endpoint. Following slow accrual of APTC events, in 2009 Pfizer proposed lowering the study power from 90% to 80%. FDA concurred with this change in 2010, when event accrual remained slow. Subsequently, with APTC event accrual still slow, in 2011 FDA agreed to increasing the non-inferiority margin for the modified intent-to-treat analysis to 1.4 from 1.33. The non-inferiority margin for the intent-to-treat analysis remained unchanged at 1.33.

2.1.2 2014 Advisory Committee Discussion and 2015 Labeling Change

While the PRECISION trial was under way, numerous epidemiological studies and meta-analyses of RCTs were conducted examining the relationship between NSAID use and CV thrombotic risk, including identifying risk factors for the adverse event. In February 2014, at a joint meeting of the Arthritis Advisory Committee (AAC) and Drug Safety and Risk Management Advisory Committee (DSaRMAC), data from the epidemiological studies and meta-analyses of RCTs were presented and the following questions were considered:

1. Do the accumulated data support a clinically significant difference in risk for CV thrombotic events for any of the NSAIDs? (discussion)

2. Do the available data support a conclusion that naproxen has a lower risk of CV thrombotic events as compared to the other NSAIDs? (Yes/No) Please discuss how your answer should be reflected in product labeling.

3. Current NSAID class labeling implies that CV thrombotic risk is not substantial with short treatment courses. Some epidemiological studies conducted since 2005 suggest that there is no, or minimal, latency period prior to the onset of CV thrombotic risk. Does the weight of evidence support reconsideration of advice regarding the latency of CV thrombotic risk? (yes/no) Provide the rationale for your perspective.

4. Based on the available data, is it appropriate to consider any restrictions or specific warnings for those populations who are at higher absolute risk for CV thrombotic events with NSAID use? (discussion) Potential options include but are not limited to extending the contraindication in certain subpopulations (e.g., patients immediately

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\(^8\) This was prior to the passage of the FDA Amendments Act in September 2007 that gave FDA the authority to require postmarket safety studies and clinical trials.
post-MI) or including a statement in the boxed warning regarding the increased absolute CV thrombotic risk in the post-MI or heart failure populations.

5. Are there are any changes that should be made to the PRECISION trial to respond to the concerns that have been raised? (discussion)

6. Discuss how the available data on CV thrombotic risk apply to “over the counter” NSAIDs at the currently available doses. What changes to OTC labeling may be warranted to refine the message about cardiovascular risk (e.g., change in description of population at risk or change in recommended duration of treatment)? (discussion)

The reader is referred to the Advisory Committee meeting minutes⁹ and transcript¹⁰,¹¹ for the full details of the discussion. Subsequently, after internal Agency discussion and consideration of the AC discussion, as well the revision of a class labeling template for the NSAIDs, a Safety Labeling Change was required for the NSAID class in July 2015 to incorporate the information drawn from the published epidemiological studies and meta-analyses and the AC discussion. An FDA Drug Safety Communication¹² was issued on the same day summarizing the labeling changes required for the NSAID class:

“Based on our review and the advisory committees’ recommendations, the prescription NSAID labels will be revised to reflect the following information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.

¹² https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm
• Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
• There is an increased risk of heart failure with NSAID use.”

The labeling required in the Safety Labeling Change notification letter was approved in May 2016 for the NSAID class.

The results of the PRECISION trial were presented at the American Heart Association meeting in November 2016 and published in the New England Journal of Medicine\textsuperscript{13} at the same time. The full clinical study report was submitted to the FDA in June 2017.

\textsuperscript{13} \url{http://www.nejm.org/doi/full/10.1056/NEJMoai1611593}
2.2  Drug interaction between nonprescription NSAIDs and low dose aspirin

2.2.1  Nonprescription Nonsteroidal Anti-inflammatory Drugs

2.2.1.1  Salicylates

Aspirin affects platelet aggregation by irreversibly inhibiting COX-1 and COX-2. Aspirin’s irreversible inhibition of COX-1 induces a defect in thromboxane A₂ (TXA₂) -dependent platelet function lasting for the lifetime of the affected platelet.

Although a few over-the-counter (OTC) aspirin products are approved and marketed under New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs), most OTC aspirin drug products are marketed under a proposed rule called the “Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Antiinflammatory (IAAA) Drug Products for OTC Human Use (53 FR 46204, November 16, 1988)” for the temporary relief of minor aches and pains associated with cold, headache, backache, toothache, premenstrual and menstrual cramps; minor pain of arthritis; and fever reduction. The salicylates allowed to be marketed OTC under the monograph are aspirin, buffered aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate. The proposed rule has not been finalized, but products conforming to the OTC monograph, including any changes to the proposed rule made since 1988, may be marketed.

Aspirin is available OTC in several dosage forms, as a tablet, buffered tablet, effervescent tablet, or caplet in immediate-release formulations and as a tablet in enteric-coated formulations in strengths ranging from 81 mg to 500 mg.

In addition to the OTC conditions of use provided for in the proposed rule referred to as the IAAA TFM in this document, FDA regulations at 21 CFR 343.80 also include professional labeling about cardiovascular uses of aspirin directed at healthcare practitioners (63 FR 56802, October 23, 1998). Professional labeling relevant to OTC drugs is labeling that provides specific information to health professionals, for uses not included in the consumers’ OTC drug labeling. An OTC monograph drug product should not have the professional labeling or any representations or claims for the professional use directly on the consumer-directed labeling. Aspirin and buffered aspirin are the only two active ingredients allowed for professional use in OTC drugs to prevent ischemic events (21 CFR 343.12). The following are the vascular and revascularization procedures indications for aspirin under professional labeling in 21 CFR 343.80:

- Vascular (ischemic stroke, transient ischemic attack, acute myocardial infarction (MI), prevention of recurrent MI, unstable angina pectoris, and chronic stable angina pectoris):


- Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli
- Reduce the risk of vascular mortality in patients with a suspected acute MI
- Reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris
- Reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris

- Revascularization Procedures (coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), and carotid endarterectomy): Aspirin is indicated in patients who have undergone revascularization procedures when there is a preexisting condition for which aspirin is already indicated.

In the IAAA TFM, FDA proposed an optional labeling statement recommending that consumers consult a physician about the other uses of aspirin, because of the potential side effects of long-term aspirin therapy (53 FR 46204, November 16, 1988). Side effects of long-term aspirin therapy may include gastrointestinal bleeding, renal failure, and hemorrhagic stroke. The specific proposed optional labeling statement information (proposed 21 CFR 324.60(f) is as follows: For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in § 343.10 (b), (c), (d), (e), and (f). The labeling may state in a prominent place the following statement: "See your doctor for other uses of" [insert name of ingredient or tradename of product], but do not use for more than 10 days without consulting your doctor because serious side effects may occur."

In addition, FDA published a proposed rule, amending the IAAA TFM, on October 20, 1993, that would require OTC drug products that contain aspirin, buffered aspirin, or aspirin in combination with an antacid to bear a statement advising consumers to consult a physician before taking these products for cardiovascular uses (58 FR 54224, October 20, 1993).

In 2017, FDA published the guidance for industry Recommended Statement for Over-the-Counter Aspirin-Containing Drug Products Labeled with Cardiovascular Related Imagery to promote the safe use of OTC aspirin drug products with cardiovascular related imagery, to include a statement that reminds consumers to talk to their doctor or healthcare provider before using aspirin for the professional indication of secondary prevention of cardiovascular events. More specifically, the guidance states that FDA does not intend to take action against manufacturers of single-ingredient aspirin, buffered aspirin, and aspirin in combination with an antacid, marketed pursuant to the TFM for IAAA Drug Products, because the product includes cardiovascular related imagery such as the heart image, if the label also includes the following statement: Talk to your doctor or other healthcare provider before using this product for your heart.
2.2.1.2 Ibuprofen

Ibuprofen, a propionic acid derivative, is a reversible inhibitor of COX-1 and COX-2. Like other NSAIDs, ibuprofen has analgesic, antipyretic, and anti-inflammatory properties. Ibuprofen was first introduced into the United States in 1974 under a new drug application (NDA) as a prescription drug indicated for the treatment of arthritic conditions. It was subsequently approved as a prescription drug under an NDA for the treatment of moderate pain in 1978. Ibuprofen was approved for OTC use under an NDA in 1984.

Nonprescription ibuprofen is indicated for the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, minor pain of arthritis; and temporary fever reduction. The recommended OTC dose of ibuprofen for adults is 200 to 400 mg every 4 to 6 hours; the maximum recommended OTC dose for adults is 1200 mg in 24 hours. Ibuprofen is widely available in a variety of strengths and formulations for children and adults as single-ingredient and combination OTC and prescription NDA and abbreviated new drug application (ANDA) drug products.

2.2.1.3 Naproxen Sodium

Naproxen is a propionic acid derivative like ibuprofen and is a reversible inhibitor of COX-1 and COX-2. Naproxen was approved under an NDA for prescription use in 1976. Naproxen sodium was approved under an NDA for prescription use in 1980. Naproxen sodium tablet, 220 mg, was approved for OTC marketing under an NDA in 1994 for temporary relief of minor aches and pains due to minor pain of arthritis, muscular aches, backache, menstrual cramps, headache, toothache; the common cold; and fever reduction.

The adult OTC dosing for naproxen sodium is 220 to 440 mg every 8 to 12 hours; the maximum recommended adult daily dose of naproxen sodium is 660 mg. Nonprescription naproxen sodium is available in adult tablet and capsule dosage forms. Naproxen sodium is available OTC in single ingredient and in combination with pseudoephedrine HCl or diphenhydramine hydrochloride.

2.2.2 Cardiovascular risk labeling and pharmacodynamic interaction between OTC NSAIDs and aspirin

When ibuprofen and naproxen were switched to OTC, there were discussions regarding the types of warning statements that should be carried from the prescription to the nonprescription label. Since then, the Agency has continually monitored postmarketing NSAID safety to ensure that labeling accurately reflects current information and conveys the benefits and risks of the drug products to patients and consumers.
2.2.2.1 1988 IAAA TFM

The following Drug Facts labeling (DFL) content language has been required for OTC aspirin products since the IAAA TFM (53 FR 46204, November 16, 1988) was published. Because of the mechanistic similarities within the NSAID class, this language is also present in ibuprofen and naproxen DFLs.

- Ask a doctor before use if you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
- Stop use and ask a doctor if
  - pain gets worse or lasts more than 10 days  
    *Comment: This language is present on products indicated for pain.*
  - fever gets worse or lasts more than 3 days  
    *Comment: This language is present on products indicated for fever.*
  - new symptoms occur

2.2.2.2 Cardiovascular Thrombotic Risk with Nonprescription Nonselective Non-Aspirin NSAIDs

Following the revisions to the prescription NSAID product labeling (see section 2.1.1), the labeling for nonprescription non-aspirin NSAIDs was revised to include more specific information about the potential CV risks and information to assist consumers in the safe use of these drugs. Specifically, nonprescription ibuprofen and naproxen labels were revised to include, “Do not use right before or after heart surgery” and “When using this product, the risk of heart attack or stroke may increase if you use more than directed or for longer than directed”. The Agency worked closely with stakeholders to encourage and review additional nonselective NSAIDs data to further evaluate the potential for increased CV risk.

2.2.2.3 Pharmacodynamic Interaction Between Ibuprofen and Aspirin

In 2005, Cryer et al published the results of a study on the effects of co-administration of ibuprofen and aspirin on thromboxane B2 (TXB2) activity, a surrogate for platelet inhibition.16 They concluded that no clinically meaningful loss of aspirin’s cardioprotection was found in the presence of ibuprofen, as reflected by TXB2 inhibition greater than 90% at all time points. However, there were additional data available at that time, including a publication by Catella-Lawson et al in 2001, indicating that ibuprofen interferes with the antiplatelet activity of low dose aspirin when they are administered concurrently.17 Based on the totality of the available data, in September 2006, FDA published a Science Paper and Healthcare Practitioner Advisory

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detailing a pharmacodynamic interaction between low dose aspirin and an OTC dose of ibuprofen. The Science Paper stated the following:

- Existing data using platelet function tests suggest there is a pharmacodynamic interaction between 400 mg ibuprofen and low dose aspirin when they are dosed concomitantly. The FDA is unaware of data addressing whether taking less than 400 mg of ibuprofen interferes with the antiplatelet effect of low dose aspirin.
- The clinical implication of this interaction may be important because the cardioprotective effect of aspirin, when used for secondary prevention of myocardial infarction, could be attenuated.
- For single doses of ibuprofen, the pharmacodynamic interaction can be minimized if ibuprofen is given at least 8 hours before or at least 30 minutes after immediate release aspirin (81mg; not enteric coated).
- The clinical implication of the interaction has not been evaluated in clinical endpoint studies.
- There are no clear data regarding the potential effect of chronic ibuprofen dosing of greater than 400 mg on the antiplatelet effect of aspirin.
- The timing of dosing of ibuprofen and low-dose aspirin is important for preserving the cardioprotective effect of aspirin.

Regarding concomitant use of OTC ibuprofen and aspirin, FDA’s Science Paper recommended the following:

- Health care providers should counsel patients about the appropriate timing of ibuprofen dosing if the patients are also taking aspirin for cardioprotective effects.
- With occasional use of ibuprofen, there is likely to be minimal risk from any attenuation of the antiplatelet effect of low dose aspirin.
- Patients taking immediate release low-dose aspirin (not enteric coated) and ibuprofen 400 mg should take the ibuprofen at least 30 minutes after aspirin ingestion, or at least 8 hours before aspirin ingestion, to avoid any potential interaction.
- Other nonselective OTC NSAIDs should be viewed as having potential to interfere with the antiplatelet effect of low-dose aspirin unless proven otherwise.
- Analgesics that do not interfere with the antiplatelet effect of low dose aspirin should be considered for populations at high risk for cardiovascular events.
- Recommendations about concomitant use of ibuprofen and enteric-coated low dose aspirin cannot be made based upon available data. One study showed that the antiplatelet effect of enteric-coated low dose aspirin is attenuated when ibuprofen 400 mg is dosed 2, 7, and 12 hours after aspirin.19

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Consistent with the Science Paper, the following DFL language was included in adult single- and combination-ingredient ibuprofen products, “Ask a doctor or pharmacist before use if you are taking aspirin for heart attack or stroke, because ibuprofen may decrease the benefit of aspirin.”

**2.2.2.4 Second cardiovascular thrombotic risk analysis of non-aspirin NSAIDs**

As described above, on February 10-11, 2014, another joint meeting of the AAC and DSaRM AC was held to discuss data and analyses published in 2006 or later that were relevant to further understanding the relationship between non-aspirin NSAIDs and CV thrombotic risk described in NSAID class labeling.\(^{20}\) See section 1.1.2 above for details of the overall discussion.

The committee was asked to discuss how the available data apply to OTC NSAIDs and what changes to OTC labeling may be warranted. As summarized in the meeting minutes:

“There was agreement among committee members that some changes to the labeling would be appropriate to make the current statements clearer in terms of their intent. They recognized that patients often take OTC products at higher doses and longer than directed despite the labeled warnings. It was stated that the risk of myocardial infarction or stroke should potentially come up higher in the labeling but must be balanced with the other important warnings. Committee members also stated that there is a lack of clarity about duration of expected use in the labeling. Some discussion also took place regarding other vulnerable populations, such as those with rheumatoid arthritis, osteoarthritis and gout, which are not specifically addressed in the labeling, and the fact that it is not clear if the CV thrombotic event risk is the same in these populations as in the patients with more traditional cardiovascular risk factors. The committee also stated that consideration needs to be given to labeling the naproxen and aspirin interaction in a way similar to how the ibuprofen and aspirin interaction is described.”

In 2017, FDA approved the following revisions to OTC DFLs for ibuprofen and naproxen adult, pediatric, single ingredient, and combination products:

- Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.
  - Comment: As the 2017 heart attack and stroke warning contained language that was similar to text which was included in ibuprofen and naproxen DFLs based on the advice of the 2005 AC (i.e., “When using this product, the risk of heart attack or stroke may increase if you use more than directed or for longer than directed”), the duplicative text was deleted when the warning was added.
- “Ask a doctor before use if you have high blood pressure, heart disease, liver cirrhosis, or kidney disease” was revised to include “or had a stroke”.
- Stop use and ask a doctor if

you have symptoms of heart problems or stroke
  - chest pain
  - trouble breathing
  - weakness in one part or side of body
  - slurring speech
  - leg swelling

OTC salicylate DFLs were not revised because aspirin and the four other salicylates available under the IAAA TFM (i.e., carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate) are not associated with increased CV risk.

2.2.2.5 Pharmacodynamic Interaction between Naproxen and Aspirin

When the FDA Science Paper was published in 2006, data regarding a potential interaction between naproxen and low dose aspirin were insufficient to make a conclusion about a pharmacodynamic interaction. The FDA Science paper referenced a study by Capone et al that suggested that naproxen may interfere with the antiplatelet activity of immediate-release aspirin when they are co-administered. However, naproxen 500 mg administered two hours before or after the administration of aspirin 100 mg did not interfere with aspirin’s antiplatelet effect. At that time, there were no data with doses of naproxen less than 500 mg.

Since 2006, additional studies evaluating the potential interaction between naproxen and low dose aspirin have become available, including studies by Oldenhof et al, Anzellotti et al, and Gurbel et al. In 2010, Oldenhof et al published their findings on the effect of maximum OTC doses of naproxen sodium or acetaminophen on low-dose aspirin inhibition of TXB2. They found that the antiplatelet effect of enteric-coated aspirin 81 mg was maintained following its co-administration with naproxen 220 mg three times a day. However, in 2011, a study by Anzellotti et al demonstrated that administration of naproxen and low-dose aspirin interferes with the irreversible inhibition of platelet COX1 by aspirin. Anzellotti et al also concluded that the interaction was smaller when naproxen is given 2 hours after aspirin. In 2017, Gurbel et al published a study that evaluated the pharmacodynamic interaction (lower bound of the one-sided 95% Confidence Interval for serum TXB2 inhibition less than 95%) between 220 mg immediate-release naproxen sodium (once or twice a day) and 81 mg immediate release aspirin daily at various dosing intervals. As stated in the article’s abstract, “There was no interaction during the first day of concurrent treatment. After 10 days, irrespective of the timing and dose of naproxen in relation to aspirin dosing, a pharmacodynamic interaction occurred which persisted after

discontinuing naproxen. In the control group (aspirin alone), the lower bound for serum inhibition was > 98% at all time points. The clinical relevance of these observations remains unknown and merits further investigation since OTC naproxen is widely used to relieve pain by individuals taking low dose aspirin for cardioprotection.”

2.2.3 Summary: Drug Facts Label Cardiovascular Language

The following DFL language is included in aspirin, ibuprofen, and naproxen labels:

- Ask a doctor before use if you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
  *Comment: For ibuprofen and naproxen labels, this language was updated to also include “or had a stroke” as part of the 2017 heart attack and stroke warning (below).*

- Stop use and ask a doctor if
  - pain gets worse or lasts more than 10 days
    *Comment: This language is present on products indicated for pain.*
  - fever gets worse or lasts more than 3 days
    *Comment: This language is present on products indicated for fever.*
  - new symptoms occur

The following additional DFL language is included in ibuprofen and naproxen labels (but not in aspirin labels):

- Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.
- Do not use right before or after heart surgery
- Ask a doctor or pharmacist before use if you are
  - under a doctor’s care for any serious condition
  - taking any other drug
- Stop use and ask a doctor if
  - you have symptoms of heart problems or stroke
    - chest pain
    - trouble breathing
    - weakness in one part or side of body
    - slurring speech
    - leg swelling
  - any new symptoms appear

The following DFL language was included in adult single- and combination-ingredient ibuprofen products based on the data described in FDA’s September 8, 2006, Science Paper:

- Ask a doctor or pharmacist before use if you are taking aspirin for heart attack or stroke, because ibuprofen may decrease the benefit of aspirin
3 Clinical Pharmacology Summary

The PRECISION trial was intended to assess cardiovascular outcomes in patients with a history of CVD or risk factors for CVD who were being treated for arthritis pain with celecoxib, ibuprofen, or naproxen. About 45% of all patients were taking concomitant aspirin. It is important to be aware of the data describing the drug interactions between each of the three NSAIDs and aspirin when considering the results of the PRECISION trial.

Aspirin is an irreversible inhibitor of COX-1 because of its acetylation of Ser529 (thereby preventing arachidonic acid from contacting Tyr385). All other NSAID inhibitors of cyclooxygenase-1 (COX-1) are reversible inhibitors of this enzyme. Propionic acid-derived non-aspirin NSAID inhibitors of COX-1, such as ibuprofen and naproxen, are thought to bind reversibly to the same platelet binding site that aspirin acetylates (Ser529). While platelet bound, ibuprofen and naproxen confer an antiplatelet effect. However, because they are reversibly bound (i.e., disassociate from the platelet as their serum concentration falls), it is possible that they interfere with the permanent antiplatelet effect of aspirin by leaving unacetylated platelets behind as they dissociate from their platelet binding sites.

3.1 Ibuprofen

The four aspirin-ibuprofen interaction studies submitted by Wyeth suggest that ibuprofen has a substantial, concentration-dependent inhibitory effect on COX-1 and can reduce thromboxane B2 (TXB2) formation in clotted blood substantially. However, ibuprofen inhibits aspirin-induced acetylation of platelets, so that unless the time of dosing is exquisitely controlled, and in some patients, even when it is exquisitely controlled, patients taking tid ibuprofen and once daily low-dose aspirin to prevent CV events may have insufficient platelet inhibition to prevent such events at trough levels of ibuprofen. In addition, the test of the interaction between multiday treatment with tid ibuprofen and once daily aspirin was performed with an immediate release chewable aspirin formulation. These results cannot be extrapolated to the use of enteric coated aspirin, which we think is the dominant form of low-dose aspirin in the US. If enteric-coated aspirin had been used in the 04-24 study instead of immediate-release aspirin, we think that the degree of inhibition of platelet function would have reduced, and an ibuprofen-aspirin interaction would have been demonstrated. See [Dr. Hariharan’s memo](#) for additional details.

3.2 Naproxen

Mechanistically, it would be reasonable to expect that naproxen (NAP) would demonstrate a similar interference with low-dose aspirin taken to prevent the occurrence of CV events in vulnerable individuals; however, the timing of the demonstrated interaction could be expected to differ from the ibuprofen interaction with low-dose aspirin due to naproxen’s longer half-life.
Bayer conducted trial 15525 to assess an interaction between aspirin and naproxen that included the following study arms:

- **Group 1** – 10 days of ASA (IR 81 mg) and NAP (220 mg QD) given concomitantly
  - Represents the reality that these drugs are frequently taken together
- **Group 2** – 10 days of NAP (220 mg QD) 30 min before ASA
  - Functions as positive control for the trial to ensure assay sensitivity if an interaction does indeed exist
- **Group 3** – 10 days of NAP (220 mg QD) administered 8 hours before ASA
  - Addresses the question regarding how many hours after an NAP dose that ASA can be taken without loss of platelet inhibition
- **Group 4** – 10 days of ASA alone
  - Functions as negative control for the trial
- **Group 5** – ASA administered 30 min before NAP (220 mg QD)
  - Addresses the question regarding how many hours after an NAP dose that ASA can be taken without loss of platelet inhibition, as well as the question as to whether NAP administered after ASA interferes with ASA’s antiplatelet effect
- **Group 6** – 10 days of NAP (220 mg bid 12 hours apart) where first dose is 30 minutes before IR ASA 81 mg qd
  - This BID dosing regimen is a potential worst case scenario for an interaction if one does indeed exist.

Corroborating FDA’s suspicions from the work of Anzellotti et al (2011), the interaction between NAP and ASA is reproducibly seen in all NAP-ASA combination treatment groups in trial 15525. The trial’s findings are remarkably internally consistent. While the interaction seems to be of a lesser magnitude when ASA is dosed 30 minutes before NAP, it is not abolished. In the circumstance of the amplified signaling systems involved in platelet activation, it is not clear that a lesser magnitude of NAP-ASA interaction measured by these PD parameters translates into fewer CV events that may result.

There are no RCT CV outcomes data assessing this interaction. However, it would be reasonable to expect that there will be a continuum of risk for CV outcome consequences of this interaction based on the background severity of the underlying cardiovascular disease, the most extreme risk groups involving those having recently experienced a CV event, those having recently undergone coronary artery bypass grafting, or those taking dual antiplatelet therapy for a recent stent implant post-acute coronary syndrome.

Trial 15525 tested 81 mg of immediate-release ASA and naproxen sodium, 220 mg qd. From a clinical standpoint, we would expect the interaction demonstrated in trial 15525 may be more prominent with enteric-coated ASA (EC-ASA) due to the lower Cmax of the enteric-coated aspirin product. The delayed absorption of enteric-coated aspirin could also make the interaction more prominent if NAP were given close to the same time as EC-ASA. We would also expect the interaction to occur with higher (prescription) doses of NAP after their discontinuation, given that the suspected mechanism of the interaction is reversible binding of NAP that competes with and prevents aspirin-mediated acetylation of platelet SER529. See Dr. Dunnmon’s memo for additional details.
3.3 Celecoxib

Celecoxib is 350 times more selective for COX-2 than COX-1, with an IC50 for the recombinant human enzymes of 0.04 μM and 15 μM, respectively (5), suggesting that interaction with aspirin’s effects on COX-1 might be minimal at concentrations that provide substantial inhibition of COX-2.

We were provided with the results of two studies that examined the effects of celecoxib on platelet function, and one study regarding its interaction with aspirin. Celecoxib 400 mg bid did not affect collagen-induced platelet aggregation in the study by Simon et al (1998). The interaction between celecoxib and aspirin was not assessed in this study. However, in the study performed by Searle, celecoxib at a dose of 200 mg q 12 hours for 4.5 days did not interfere with inhibition of COX-1 by aspirin 325 mg given at the same time as the last dose of celecoxib. In the absence of clinical data, a modest interaction with low-dose aspirin (81mg) when initiated on a background of celecoxib cannot be ruled out. Nevertheless, any interaction with celecoxib is still not expected to last beyond the initial few days upon low-dose aspirin initiation, because aspirin at 81 mg is still more than what is required to cause maximal inhibition of serum TxB2 (7). Also, for the same reason, we might not expect any meaningful interaction in a scenario where celecoxib is initiated in a patient on chronic low-dose aspirin. See Dr. Hariharan’s memo for additional details.
4 Clinical Safety Summary (PRECISION)

4.1 Study Design

4.1.1 Main study

PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen) was a randomized, double-blind, triple-dummy, multicenter, 3-arm parallel-group non-inferiority trial of cardiovascular safety in OA or RA patients with or at high risk for CVD comparing celecoxib with naproxen and ibuprofen.

The study was conducted from October 4, 2006 to April 12, 2016 at 949 centers in 14 countries globally.

Eligibility for enrollment included the following key criteria:

Key Inclusion Criteria
1. Men and women, 18 years of age or older, with clinical diagnosis of OA or RA with a duration of at least 6 months.
2. Receiving a chronic analgesic regimen for at least 6 months and taking chronic analgesic therapy ≥50% of the time.
   a. Subjects achieving adequate pain management with acetaminophen were not eligible
   b. In the investigator’s opinion, the subject required and was eligible for chronic, daily therapy with NSAID to control arthritis signs and symptoms
   c. RA subjects receiving disease-modifying anti-rheumatic drug (DMARD) or oral corticosteroids were required to be on the same DMARD or corticosteroid for 3 months and on a stable dosing regimen for 1 month prior to enrollment
3. Subject with established or at high risk for CVD defined as one of the following:
   a. Coronary disease
      • History of stable angina; or
      • History of MI, unstable angina (UA), percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery at least 3 months prior to randomization; or
      • An angiographic stenosis greater than 50% by visual estimation at catheterization.
   b. Occlusive disease of non-coronary arteries
      • History of transient ischemic attack (TIA) or ischemic stroke at least 3 months prior to randomization, or
      • Angiographic or ultrasound diagnosis of carotid artery stenosis ≥50%, or
      • History of carotid endarterectomy at least 3 months prior to randomization, or
      • Symptomatic peripheral arterial disease (e.g., intermittent claudication), or
      • Other arterial surgery or angioplasty for atherosclerotic vascular disease at least 3 months prior to randomization
   c. Diabetes mellitus: clinical diagnosis of Type I or Type II diabetes.
      • Females were to require current insulin treatment.
Males could have Type I or Type II with or without insulin therapy.

d. High risk of atherosclerotic vascular disease

• Females required at least 2 of the following 3:
  - Age ≥65 years
  - History of hypertension (HTN)
  - Current smoking (defined as any cigarette smoking within the past 30 days).

• Males required at least 3 of the following:
  - Age >55 years
  - History of hypertension
  - History of dyslipidemia (defined as low density lipoprotein (LDL) >160 mg/dL [4.144 mmol/L] or high-density lipoprotein (HDL) <35 mg/dL [0.906 mmol/L]). Subjects currently undergoing lipid lowering therapy with a statin drug, fibrate, prescription omega-3-acid ethyl esters (e.g., Omacor®, Lovaza™) or prescription niacin (≥1000 mg/day) automatically met this criterion
  - Family history of premature CVD (defined as history of MI, angina pectoris, heart failure, cardiac death or coronary revascularization; did NOT include history of HTN), stroke, carotid endarterectomy, or other arterial surgery or angioplasty for atherosclerotic vascular disease in a parent, grandparent, or sibling with first symptom onset or diagnosis before age 55 years for males and 65 years for females
  - Current smoking (defined as any cigarette smoking within the past 30 days)
  - History of microalbuminuria, urine protein/creatinine ratio >2
  - Left ventricular hypertrophy (LVH) as evidenced by electrocardiogram (ECG) or echocardiography
  - Documented Ankle-Brachial Index (ABI) <0.9
  - Waist Hip Ratio (WHR) ≥0

Key Exclusion Criteria
1. Documented MI or stroke within 3 months prior to randomization.
2. CABG surgery, or any major surgery (cardiac or non-cardiac) within 3 months.
3. Planned coronary, cerebrovascular, or peripheral revascularization at the time of study screening; in case of planned revascularization, the subject could be re-screened no sooner than 3 months after revascularization.
4. Unstable condition defined as any of the following:
   a. UA within 3 months
   b. Uncontrolled HTN (defined as systolic blood pressure [SBP] greater than 140 mmHg and/or diastolic blood pressure [DBP] greater than 90 mmHg)
5. Cardiac electrophysiologic instability including uncontrolled complex ventricular arrhythmia, uncontrolled atrial fibrillation or flutter, or uncontrolled supraventricular tachycardia within 3 months. The presence of an implantable defibrillator was not a contraindication.
6. New York Heart Association (NYHA) Class III or IV congestive heart failure (CHF) or known left ventricular dysfunction with ejection fraction ≤35%.
7. Diagnosed with or had been treated for esophageal, gastric, pyloric, or duodenal ulceration within 60 days.
8. History of GI perforation, obstruction, or bleed within 6 months.
9. Other known, active, significant GI, hepatic, renal, or coagulation disorders.
10. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or blood urea nitrogen (BUN) exceeding 2.0 times the upper limit of normal (ULN); creatinine exceeding 1.7 mg/dL (150 μmol/L) in men or 1.5 mg/dL (133 μmol/L) in women.
11. Active malignancy of any type.

After screening, eligible subjects were randomized (N=24081) to one of the following treatment groups:
- Celecoxib 100-200 mg bid (n=8072 randomized, n=8030 treated)
- Ibuprofen 600-800 mg tid (n=8040 randomized, n=7992 treated)
- Naproxen 375-500 mg tid (n=7969 randomized, n=7933 treated)

At randomization, all subjects received the lowest dose strength of the active treatment to which they were assigned, either celecoxib 100 mg bid, ibuprofen 600 mg tid, or naproxen 375 mg bid. At subsequent visits, investigators could increase the dose of ibuprofen to 800 mg tid, or the dose of naproxen to 500 mg bid for subjects who failed to achieve adequate pain management of their arthritis. Dose adjustments (increase or decrease) at all subsequent study visits, within the dosing range mandated by the protocol were allowed. The protocol specified that “subjects should always be maintained on the lowest effective dose within the dosing range mandated by this protocol.”

Regarding the celecoxib dose in this study, in accordance with approved labeling in many regions of the world (including the U.S.), the maximum dose of celecoxib for the OA subjects, which comprised 90% of the study population, was limited to 200 mg per day, administered as 100 mg bid. In countries where celecoxib 200 mg bid is allowed by labeling for OA, subjects could receive upward dose titration if warranted by the need for greater efficacy. All RA subjects (10% of the study population) received celecoxib 100 mg bid with upward titration up to 200 mg bid as needed, consistent with global labeling.

Subject randomization was stratified according to the primary diagnosis (either OA or RA) and aspirin (ASA) use for CV prophylaxis at baseline. Subjects already taking aspirin less than or equal to 325 mg/day were allowed to continue aspirin regardless of their CV risk profile. During the study, subjects with a high relative CV risk were evaluated for the need for antiplatelet therapy, and low-dose aspirin was introduced at the discretion of the investigators. Additionally, all randomized subjects were provided with a gastroprotective agent (e.g., proton pump inhibitor, histamine-2 blocker). Subjects enrolled in the study received preventive care for CVD, according to the local standards and/or guidelines including but not limited to: aspirin, statins, angiotensin converting enzyme (ACE)-inhibitors, beta-blockers, other antiplatelet agents, and antihypertensive medications. Subjects with RA were allowed to continue their stable (same medications for 3 months and same dose for 1 month) traditional or biologic disease-modifying anti-rheumatic drugs (DMARDs).
Treatment with the following medications was specifically excluded during the study:

- Over-the-counter and prescription NSAIDs and COX-2 selective inhibitors (other than aspirin ≤ 325 mg/day)
- Aspirin > 325 mg/day
- Warfarin and other vitamin K antagonist anticoagulants
- Oral corticosteroids at a daily dose greater than 20 mg prednisone or equivalent
- Lithium

The following rescue medications were allowed for breakthrough arthritis pain:

- Acetaminophen or non-NSAID combination product
- Any opioid including tramadol
- Duloxetine
- Intra-articular steroid or hyaluronic acid

In response to an IR, the Applicant indicated that such concomitant pain therapies were not specifically prohibited, and that patients could remain on them if they were already on them at baseline.

It was required that subjects who prematurely discontinued study drug treatment not be treated with open-label celecoxib, naproxen, or ibuprofen for 30 days following discontinuation of study drug therapy. In addition, it was strongly recommended that subjects not be treated with any open-label NSAID or COX-2 selective inhibitors, but be managed with the rescue therapy allowed (described above) during study follow-up through completion of the study.

Following randomization, clinic visits were completed at Months 1, 2, 4, 8, and 12, and every 6 months thereafter through 42 months. Subjects were contacted by telephone 30 days after the End of Study.

Safety assessments included physical examination, vital signs, clinical laboratory evaluations, and ECG at pre-specified time points.

If a subject was noted to have HTN or a worsening of existing HTN, BP measurements were repeated within 2 weeks. If the increase in BP was confirmed, the subject was treated according to the clinical judgment of the investigator and applicable practical guidelines. Subjects were required to permanently discontinue study drug therapy if their HTN was unable to be controlled within a 3-month time period of treatment. Newly diagnosed HTN and worsening of existing HTN were reported as adverse events (AEs).

Pre-specified criteria for permanent study drug discontinuation included the following:

- Experienced asthma or allergic-type reactions
- New onset NYHA Class III or IV CHF or known left ventricular dysfunction with ejection fraction ≤35%
- New onset of AST, ALT, or BUN exceeding 2.0 times the ULN; creatinine exceeding 1.7 mg/dL (150 μ mol/L) in men or 1.5 mg/dL (133 μ mol/L) in women.
- Experienced an APTC primary endpoint
• Experienced clinically significant CV, renal, GI, and/or anemia study endpoints as per investigator discretion
• Need for chronic treatment (defined as >3 months) with warfarin
• Need for treatment with lithium
• Inability to effectively control HTN
• Surgical treatment for arthritis obviating the need for chronic, daily NSAID treatment

Blinded adjudication of all CV (including hospitalization for hypertension), GI, and renal events in accordance with pre-specified definitions was performed by separate independent adjudication committees. Monitoring of CV, GI, renal, and overall safety was performed by an independent data monitoring committee.

Pre-defined definitions for adjudication of CV, renal, GI, and anemia events:

• Antiplatelet Trialists Collaboration (APTC) Events were defined as a composite of all of the following:
  o Death due to CV causes (including cardiac, cerebrovascular, venous thromboembolic, hemorrhagic, other vascular, or unknown cause)
  o Non-fatal MI
  o Non-fatal stroke (including intracranial hemorrhages, stroke of ischemic or unknown etiology)

• Clinically Significant Cardiovascular and Renal Events included the following:
  o Hospitalization for UA
  o Revascularization
  o Hospitalization for CHF
  o Hospitalization for hypertension
  o Hospitalization for TIA
  o Renal insufficiency or failure

• Renal events included a composite of predefined rises in creatinine levels [verified serum creatinine of ≥2.0mg/dL (177μmol/L) and an increase of ≥0.7mg/ml (62μmol/L)], or hospitalization for acute renal failure (defined as a doubling in serum creatinine, or confirmation of hyperkalemia with ≥ 50% elevation in serum creatinine), or the initiation of hemodialysis or peritoneal dialysis.

• Clinically Significant Gastrointestinal Events (CSGIEs) included the following:
  o Gastroduodenal (GD) hemorrhage
  o Gastric outlet obstruction
  o GD, small bowel, or large bowel perforation
  o Large bowel hemorrhage
  o Small bowel hemorrhage
  o Acute GI hemorrhage of unknown origin, including presumed small bowel hemorrhage
  o Symptomatic gastric or duodenal ulcer
Clinically Significant Iron Deficiency Anemia of GI Origin:
All cases of anemia were adjudicated by the Clinical events committee (CEC). Investigators were encouraged to ensure that subjects with anemia of non-GI sources were excluded by evaluation of hematologic parameters.

The primary endpoint was the occurrence of an adjudicated event that met Antiplatelet Trialists Collaboration (APTC) criteria, i.e., the composite of death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke.

- The intent-to-treat (ITT) analysis set consisted of all randomized subjects. Subjects in the ITT population were analyzed as randomized.
- The modified intent-to-treat (mITT) analysis set consisted of all randomized subjects who received at least one dose of study drug, and had at least one post-baseline visit. Subjects in the mITT population were analyzed as randomized.

The study continued until the required 580 APTC composite endpoints for the intent-to-treat (ITT) analysis and 420 for the modified ITT (mITT) analysis had been reached or exceeded25, and all subjects had had the opportunity for 18 months follow-up. All subjects who discontinued study drug treatment prematurely were continued to be followed through Month 42 or the completion of the study, whichever occurred first.

The primary hypothesis tested in PRECISION was that celecoxib was non-inferior to naproxen for the APTC composite endpoint, assessed in a time-to-event analysis using a Cox Proportional Hazards model. Hypotheses also tested were whether ibuprofen was non-inferior to naproxen and whether celecoxib was non-inferior to ibuprofen for the APTC composite endpoint.

Renal, gastrointestinal (GI), all-cause mortality, and additional outcomes of cardiovascular safety were assessed as secondary or tertiary endpoints in PRECISION. Despite the lack of a pre-specified hierarchical statistical testing plan, the Applicant conducted statistical testing for these outcomes and reported nominal confidence intervals and p-values. Therefore, the results of these statistical tests should only be considered exploratory, and the data interpreted descriptively.

4.1.2 ABPM substudy

As part of PRECISION, a 4-month substudy focusing on the effects of the three drugs on BP as measured by ambulatory monitoring (ABPM substudy) was conducted. Five hundred and forty-five male and female PRECISION participants from 60 clinical centers in the United States were enrolled in the study, and 444 subjects were included in the analysis.

The doses of all three medications could be titrated up from lower to higher dose at Visit 4 (Month 2). However, based on the regulatory approved dose range, patients with OA in the celecoxib arm remained on the 100 mg bid dose.

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25 Refer to section 6.2.2 for the censoring rules for the ITT and mITT populations
The duration of participation was a total of 4 months with **24-hr ABPM recording** performed at baseline (**Baseline**), 2 months post randomization (PRECISION Visit 4 or **Month 2**), 4 months post randomization (PRECISION Visit 5 or **Month 4**) and **Premature Study Drug Discontinuation** for subjects who discontinued study therapy prior to Visit 5/Month 4.

ABP measurements were obtained using a SpaceLabs 90207 monitor provided by Integrium. Integrium’s central ABPM reading laboratory performed the ABPM data collection, reading, and quality evaluation for the PRECISION Study database. ABP was measured every 20 minutes during daytime (06:00 to 21:59 h), and every 30 minutes during nighttime (22:00 to 05:59 hours).

The primary endpoint for the substudy was the change in 24-hour mean ambulatory systolic blood pressure (SBP) at Month 4 compared with baseline.

Secondary endpoints included the following:
- Change in mean 24-hour SBP at Month 2
- Change in mean 24-hour diastolic DBP at Months 2 and 4
- Change mean 24-hour mean arterial pressure (MAP) at Months 2 and 4
- Change in mean 24-hour pulse pressure (PP) at Months 2 and 4
- Change in Awake (6:00 - 21:59 h) SBP and DBP at Months 2 and 4
- Change in Sleep (22:00 – 05:59 h) SBP and DBP at Months 2 and 4

### 4.1.2.1 Statistical analysis

A sample of 117 subjects per arm was needed to detect a 3-mmHg difference between any two treatment groups (assuming a standard deviation of 7.5 mmHg with Bonferroni adjustment for multiplicity), with 80% power and at the 0.0167 (0.05/3) level of significance. Assuming a 35% drop-out rate, the study required randomizing 180 subjects per arm (for a total of 540).

The primary analysis, Analysis of Covariance (ANCOVA) mITT, was performed to model the effect of treatment on the change in SBP24h with baseline SBP24h and BMI as covariates. Pair-wise comparisons were performed comparing the least squares (LS) mean of each of the three treatment groups. Each comparison was considered statistically significant if the p-value was <0.0167.

The sub-study mITT population consisted of all randomized subjects with valid ABP data for analyses, excluding subjects missing ABPM recording at baseline and subjects with a baseline ABPM recording but with no follow-up ABPM recordings.

For subjects who discontinued study drug prior to Month 2, measurements taken at the time of discontinuation were used as the Month 2 measurement. Similarly, measurements taken at the time of discontinuation at or after Month 2 were used as the Month 4 measurement. As a sensitivity analysis to evaluate the potential effect of missing data, the primary analysis was repeated using the mixed measure repeated measurement (MMRM) model.
All secondary endpoints of changes in BP, similar to the primary endpoint, were analyzed using an ANCOVA model based on the mITT population. Two-sided tests were performed for the secondary endpoints at the 0.05 significance level.

The relationship between change in BP and APTC composite CV endpoint, as well as its components, was analyzed in a Cox proportional hazard model, using time to the 1st APTC composite endpoint or one of its components as the dependent variable. The independent variables included treatment, region, blood pressure at Month 4 or change from baseline in BP at Month 4. Baseline BP and BMI were included as covariates in the model. Subjects with APTC events that occurred prior to Month 4 were excluded for these analyses.

4.2 Study Results

4.2.1 Main study

4.2.1.1 Study Subjects Baseline Characteristics

The majority of the study population was comprised of white female subjects with OA. There were no major differences between treatment groups in the baseline characteristics, including age, weight, BP, key laboratory parameters, CV risk factors, medical history, aspirin use, and smoking history. The baseline median Visual Analog Scale (100 mm VAS) pain score of for the arthritis pain for all three treatment groups was 56 (0-100 range), defining patients with moderate pain.

The male subjects in the study numbered 8636 compared to 15,445 female subjects. The majority of the subjects were White (75%). The mean (±SD) age for all subjects was 63 ± 9.4 years with most subjects aged between 45 to 64 years (52%). The predominant arthritic condition was OA, occurring in 90% of the subjects, which, by labeling, determined the dose of 100 mg bid of celecoxib to be administered in those subjects. The mean duration since first diagnosis of OA and RA was 10.3 years and 10.9 years, respectively. The median (range) weight, BMI, and height were: 86.6 kg (26.4-249.4), 31.4 kg/m² (12.1-89.5), and 165 cm (122-213), respectively.

There were no differences in CV risk factors and durations of primary diagnoses between the three treatment groups.

The majority of the subjects (77%) had high risk of CVD but with no evidence of overt CVD (referred to in the clinical study report as “primary prevention subjects”).

Approximately 78% of the subjects in all treatment groups had a history of HTN, 62% had a history of dyslipidemia, and 54% used statins. The mean (±SD) systolic BP in mmHg was 125 ± 10 in all treatment groups with median of 127 (78-210 range) for celecoxib, 127 (75-175 range) for ibuprofen, and 126 (64-177 range) for naproxen. Baseline DMARD use was reported by 7% in all treatment groups.

As shown in Table 1, the use of aspirin and smoking classification were balanced between the treatment groups. Aspirin usage was reported in 46% of subjects in each treatment arm. Approximately 46% of all subjects never smoked, 34% were ex-smokers, and 20% were actively smoking.
Table 1: Use of aspirin and smoking classification at baseline (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib (N=8072)</th>
<th>Ibuprofen (N=8040)</th>
<th>Naproxen (N=7969)</th>
<th>Total (N=24081)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline aspirin use, n%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3701 (46%)</td>
<td>3712 (46%)</td>
<td>3652 (46%)</td>
<td>11065 (46%)</td>
</tr>
<tr>
<td>No</td>
<td>4371 (54%)</td>
<td>4328 (54%)</td>
<td>4317 (54%)</td>
<td>13016 (54%)</td>
</tr>
<tr>
<td><strong>Smoking classification, n%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>3647 (45%)</td>
<td>3652 (45%)</td>
<td>3657 (46%)</td>
<td>10956 (46%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>2729 (34%)</td>
<td>2699 (34%)</td>
<td>2674 (34%)</td>
<td>8102 (34%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>1689 (21%)</td>
<td>1680 (21%)</td>
<td>1631 (21%)</td>
<td>5000 (21%)</td>
</tr>
</tbody>
</table>

(Source: Adapted from Applicant’s Table 9 from clinical study report)

4.2.1.2 Subjects Disposition

A total of 31,857 subjects were screened, of which 24,222 were randomized. Some of the randomized subjects were not unique. Thirty-five randomizations were from 32 subjects who enrolled more than once (29 subjects were enrolled twice and 3 subjects were enrolled three times), and 106 subjects were determined to be inappropriately enrolled; therefore, the total number of randomized subjects was actually 24,081 (ITT population), of which 23,955 were treated and 23,953 were treated and had at least one post-baseline visit (mITT population). Of the 24,081 randomized subjects, 16,865 (70%) completed the study.

Upon review of the reasons for discontinuations, it was noted that three general categories, “no longer willing to participate in study”, “other”, and “withdrew consent”, accounted for a substantial proportion of the discontinuations from treatment and from study. A spot-check review identified subjects who were coded as discontinued from study due to “other” or “no longer willing to participate” categories although the reason described by the investigator was an AE, such as uncontrolled HTN or revascularization. For discontinuations from treatment, cases coded to the same non-specific broad categories were identified for which investigators described lack of efficacy and AEs (e.g., kidney test abnormalities, revascularization). When questioned, the Applicant explained that, “Per study design, subjects were to be monitored after discontinuation of the study treatment, for as long as possible, ideally until completion of the study participation (42 months). Subjects who discontinued treatment for an Adverse Event or for Insufficient Clinical Response were to continue their participation in the study, off treatment, via office visits, phone visits, or periodic review of their medical records. An option to be contacted only once at the end of the study (42 months) was also available for subjects unable to comply with the visit schedule. It was anticipated that, given all the options to continue in the study off treatment, discontinuations from the study due to Adverse Events, Insufficient Clinical Response, Pregnancy, or Protocol Violations would not occur. As such, the End of Study CRF page did not include these options.”

This explanation did not adequately respond to the Division’s concerns about misclassification or undercounting of adverse events. The Division asked the Applicant to reclassify discontinuations...
appropriately, applying the full set of reasons to both discontinuation from treatment and discontinuation from study.

Table 2 illustrates patient disposition from study and treatment with numbers reflecting the reclassification results. Subjects who were never treated (N=126) were excluded from this analysis. Compared to the disposition table included in the original sNDA application, there was redistribution of the numbers. However, the redistribution was balanced between the three treatment groups, and the numbers were too small to result in meaningful changes in the outcome results. However, with the reclassification, some of the reasons for discontinuation from study were due to AEs or insufficient clinical response, reasons that had not been allowed for in the CRF.

**Table 2: Subject Discontinuations from Study and Treatment with Reasons for Discontinuation - Reclassified (safety population)**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Celecoxib 100-200 mg bid N (%)</th>
<th>Ibuprofen 600-800 tid N (%)</th>
<th>Naproxen 375-500 mg bid N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assigned to treatment</td>
<td>8072</td>
<td>8040</td>
<td>7969</td>
<td>24081</td>
</tr>
<tr>
<td>Treated</td>
<td>8030</td>
<td>7992</td>
<td>7933</td>
<td>23955</td>
</tr>
<tr>
<td>Completed study</td>
<td>5655 (70%)</td>
<td>5571 (70%)</td>
<td>5612 (71%)</td>
<td>16838 (70%)</td>
</tr>
<tr>
<td>Discontinued treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject died</td>
<td>62 (0.8%)</td>
<td>83 (1%)</td>
<td>93 (1.2%)</td>
<td>238 (1%)</td>
</tr>
<tr>
<td>Does not meet entrance criteria</td>
<td>40 (0.5%)</td>
<td>51 (0.6%)</td>
<td>33 (0.4%)</td>
<td>124 (0.5%)</td>
</tr>
<tr>
<td>Insufficient clinical response</td>
<td>826 (10.3%)</td>
<td>724 (9.1%)</td>
<td>693 (8.7%)</td>
<td>2243 (9.4%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>444 (5.5%)</td>
<td>435 (5.4%)</td>
<td>416 (5.2%)</td>
<td>1295 (5.4%)</td>
</tr>
<tr>
<td>Medication error without AE</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No longer willing to participate</td>
<td>1337 (16.7%)</td>
<td>1214 (15.2%)</td>
<td>1249 (15.7%)</td>
<td>3800 (15.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>721 (8.9%)</td>
<td>752 (9.4%)</td>
<td>743 (9.4%)</td>
<td>2216 (9.3%)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>76 (1%)</td>
<td>71 (0.9%)</td>
<td>66 (0.8%)</td>
<td>213 (0.9%)</td>
</tr>
<tr>
<td>Study terminated by Sponsor</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Adverse event</td>
<td>1818 (22.6%)</td>
<td>2221 (27.8%)</td>
<td>2036 (25.7%)</td>
<td>6075 (25.4%)</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Investigator declined further participation</td>
<td>25 (0.3%)</td>
<td>19 (0.2%)</td>
<td>17 (0.2%)</td>
<td>61 (0.3%)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>10 (0.1%)</td>
<td>13 (0.2%)</td>
<td>13 (0.2%)</td>
<td>36 (0.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discontinued study</th>
<th>2316 (29%)</th>
<th>2365 (30%)</th>
<th>2262 (29%)</th>
<th>6943 (29%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject died</td>
<td>189 (2.3%)</td>
<td>190 (2.4%)</td>
<td>227 (2.9%)</td>
<td>606 (2.5%)</td>
</tr>
<tr>
<td>Does not meet entrance criteria</td>
<td>15 (0.2%)</td>
<td>13 (0.2%)</td>
<td>11 (0.1%)</td>
<td>39 (0.2%)</td>
</tr>
<tr>
<td>Investigator declined further participation</td>
<td>84 (1%)</td>
<td>80 (0.9%)</td>
<td>64 (0.8%)</td>
<td>228 (1%)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>632 (7.9%)</td>
<td>616 (7.7%)</td>
<td>560 (7%)</td>
<td>1808 (7.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>165 (2.1%)</td>
<td>193 (2.4%)</td>
<td>175 (2.2%)</td>
<td>533 (2.2%)</td>
</tr>
<tr>
<td>Study terminated by Sponsor</td>
<td>10 (0.1%)</td>
<td>4</td>
<td>8 (0.1%)</td>
<td>22 (0.1%)</td>
</tr>
<tr>
<td>No longer willing to participate</td>
<td>534 (6.7%)</td>
<td>539 (6.7%)</td>
<td>530 (6.9%)</td>
<td>1603 (6.7%)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>658 (8.2%)</td>
<td>685 (8.6%)</td>
<td>648 (8.2%)</td>
<td>1991 (8.3%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>27 (0.3%)</td>
<td>41 (0.5%)</td>
<td>36 (0.5%)</td>
<td>104 (0.4%)</td>
</tr>
<tr>
<td>Insufficient clinical response</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

(Source: Applicant’s Table 3.2 from response to information request submitted January 12, 2018)

Overall, 16,308 (68%) subjects discontinued from treatment, and 6,943 (29%) subjects discontinued from the study for reasons overall balanced between the three treatment groups. Discontinuations from treatment and study due to death were balanced between treatment groups. A larger proportion of subjects from the celecoxib group discontinued from treatment due to insufficient clinical response compared to ibuprofen and naproxen, 10.3%, 9%, and 8.7% respectively. In contrast, a smaller proportion of subjects from the celecoxib group discontinued due to AE compared to ibuprofen and naproxen, 23%, 28%, and 26%, respectively. The higher treatment discontinuation rate due to AEs and the lower treatment discontinuation rate due to insufficient clinical response in the comparator drugs relative to the celecoxib, may be explained by the lower doses administered in the celecoxib group and the higher doses administered in the ibuprofen and naproxen groups.
4.2.1.3 Exposure to Study Drug

The duration of treatment (Table 3) was similar among the treatment groups, with an overall mean of 20 months. The median exposure was 18 months for celecoxib (range: 0-51 months) and naproxen (range: 0-82 months), whereas it was slightly shorter for ibuprofen (16 months; range: 0-58 months). Approximately 60% of the subjects, with no meaningful difference between treatment groups, stayed on treatment for 1 year, 40% for 2 years, and 30% for 3 years.

Table 3: Duration of treatment (ITT)

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Celecoxib 100-200 mg</th>
<th>Ibuprofen 600-800 mg</th>
<th>Naproxen 375-500 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= 1 Day</td>
<td>8010 (99.5)</td>
<td>7992 (99.4)</td>
<td>7913 (99.5)</td>
<td>23055 (99.5)</td>
</tr>
<tr>
<td>&gt;= 1 Month</td>
<td>7424 (92.0)</td>
<td>7348 (91.4)</td>
<td>7351 (92.2)</td>
<td>22123 (91.9)</td>
</tr>
<tr>
<td>&gt;= 3 Months</td>
<td>6608 (81.8)</td>
<td>6373 (78.3)</td>
<td>6523 (83.9)</td>
<td>19504 (83.0)</td>
</tr>
<tr>
<td>&gt;= 6 Months</td>
<td>5929 (72.2)</td>
<td>5566 (69.2)</td>
<td>5754 (72.2)</td>
<td>17149 (71.2)</td>
</tr>
<tr>
<td>&gt;= 9 Months</td>
<td>5220 (64.7)</td>
<td>4934 (61.4)</td>
<td>5094 (63.9)</td>
<td>15248 (63.3)</td>
</tr>
<tr>
<td>&gt;= 12 Months</td>
<td>4857 (60.2)</td>
<td>4494 (55.9)</td>
<td>4699 (59.0)</td>
<td>14051 (58.3)</td>
</tr>
<tr>
<td>&gt;= 18 Months</td>
<td>4105 (50.9)</td>
<td>3801 (47.3)</td>
<td>3988 (56.0)</td>
<td>11804 (49.4)</td>
</tr>
<tr>
<td>&gt;= 24 Months</td>
<td>3338 (41.4)</td>
<td>3050 (37.9)</td>
<td>3209 (40.3)</td>
<td>9597 (39.9)</td>
</tr>
<tr>
<td>&gt;= 30 Months</td>
<td>2782 (34.5)</td>
<td>2550 (31.7)</td>
<td>2610 (33.6)</td>
<td>8090 (33.3)</td>
</tr>
<tr>
<td>&gt;= 36 Months</td>
<td>2249 (27.9)</td>
<td>2093 (26.0)</td>
<td>2157 (27.1)</td>
<td>6497 (27.0)</td>
</tr>
<tr>
<td>&gt;= 42 Months</td>
<td>1783 (22.3)</td>
<td>1608 (20.0)</td>
<td>1715 (21.5)</td>
<td>5106 (21.2)</td>
</tr>
<tr>
<td>&gt;= 42 Months</td>
<td>630 (7.8)</td>
<td>590 (7.3)</td>
<td>564 (7.1)</td>
<td>1784 (7.4)</td>
</tr>
</tbody>
</table>

(Source: Applicant’s table 14.4.1.1.1 from study report body 11, page 74)

About 1/3 of patients stayed on study drug treatment for at least some duration following an APTC event despite the protocol-specified requirement for discontinuation of treatment at the time of an APTC event. As illustrated below, about 20% of patients with an APTC event stayed on study drug treatment for longer than 1 month after the event occurred. A total of 307 APTC events occurred on treatment:

- 194 (63%) discontinued the active treatment on the same day as the APTC event
- 33 (11%) discontinued the active treatment 1-10 days after an APTC event
- 20 (6%) discontinued the active treatment 11-30 days after an APTC event
- 19 (6%) discontinued the active treatment 31-100 days after an APTC event
- The other 41 (13%) scattered from 101 days to 1135 days

The average daily dose in mg (mean ± SD) was 209 ± 37 for celecoxib, 2045 ± 246 for ibuprofen, and 852 ± 103 for naproxen. Table 4 presents the average dose for all subjects and for subjects with RA.
Study subjects in all three treatment groups were allowed to dose escalate if the pain relief was not satisfactory. However, the celecoxib labeling restricts the dose for OA to 100 mg bid and allows the 200 mg bid dose for RA patients only. The ibuprofen and naproxen labels do not have recommendations or dose restrictions for specific pain conditions. Given that 90% of the study population was comprised of OA patients, and following the labeling recommendations, only ~6% of the subjects in the celecoxib group had dose escalation compared to ~55% of the subjects in the ibuprofen and naproxen treatment groups.

When the dose escalation was further assessed by duration of exposure to the higher dose, a higher proportion of subjects were exposed to the higher dose for over one year compared to <3 months, <6 months, and <1 year of treatment, as illustrated in Table 5.
### Table 5: Proportion of subjects with dose escalation by duration of exposure (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Subjects on celecoxib 200 mg bid (Continuous exposure)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>1 day &lt; 3 mo</td>
<td>≥ 3 mo to &lt; 6 mo</td>
<td>≥ 6 mo to 1 yr</td>
</tr>
<tr>
<td>Overall</td>
<td>8072</td>
<td>470 (6%)</td>
<td>79 (1%)</td>
<td>55 (0.7%)</td>
</tr>
<tr>
<td></td>
<td>N (%) with dose escalation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>7259</td>
<td>17 (0.2%)</td>
<td>6 (0.1%)</td>
<td>3 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>N (%) with dose escalation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>813</td>
<td>453 (56%)</td>
<td>73 (9%)</td>
<td>52 (6%)</td>
</tr>
</tbody>
</table>

|                  | Subjects on ibuprofen 800 mg tid (Continuous exposure) |               |               |               |
|                  | N                                                      | 1 day < 3 mo  | ≥ 3 mo to < 6 mo | ≥ 6 mo to 1 yr |
| Overall          | 8040                                                   | 4416 (55%)    | 789 (10%)     | 513 (6%)      | 765 (10%)     | 2349 (29%)   |
|                  | N (%) with dose escalation                             |               |               |               |
| OA               | 7208                                                   | 3946 (55%)    | 685 (10%)     | 465 (7%)      | 691 (10%)     | 2105 (29%)   |
|                  | N (%) with dose escalation                             |               |               |               |
| RA               | 832                                                    | 470 (57%)     | 104 (13%)     | 48 (6%)       | 74 (9%)       | 244 (29%)    |

|                  | Subjects on naproxen 500 mg bid (Continuous exposure) |               |               |               |
|                  | N                                                      | 1 day < 3 mo  | ≥ 3 mo to < 6 mo | ≥ 6 mo to 1 yr |
| Overall          | 7969                                                   | 4369 (55%)    | 661 (8%)      | 520 (7%)      | 789 (10%)     | 2399 (30%)   |
|                  | N (%) with dose escalation                             |               |               |               |
| OA               | 7178                                                   | 3937 (55%)    | 598 (8%)      | 471 (7%)      | 706 (10%)     | 2162 (30%)   |
|                  | N (%) with dose escalation                             |               |               |               |
| RA               | 791                                                    | 432 (55%)     | 63 (8%)       | 49 (6.2%)     | 83 (10.5%)    | 237 (30%)    |

(Source: Adapted from Applicant’s tables from response to information request submitted January 12, 2018)

### 4.2.1.4 Use of NSAID, Aspirin, Gastroprotective Agent, and Rescue Medication During Study

- **“Cross-in” NSAIDs**
  During a period of substantial concomitant use of ibuprofen, naproxen, or celecoxib that were not study medications for ≥7 consecutive days, subjects were considered to be on “cross-in” treatment. Despite not being allowed by the protocol, while on study treatment or during the 30 days immediately following treatment discontinuation, 2153 (8.9%) subjects took concomitant celecoxib, naproxen, and ibuprofen that were not assigned as study medications (cross-in). The
rate of cross-in was similar across treatment groups: 8.7% of the subjects in the naproxen group, and 9% of the subjects, each in the celecoxib and ibuprofen groups.

The Applicant conducted post-hoc analyses summarizing the NSAID use according to four broad categories: celecoxib, ibuprofen, naproxen, and ‘other’ during the study, before treatment discontinuation, and after treatment discontinuation (see Table 6).

**Table 6: Summary of “Cross-in” NSAID use during study**

<table>
<thead>
<tr>
<th>NSAID Category</th>
<th>Before Treatment Discontinuation</th>
<th>After Treatment Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Number (%) of Subjects With Any Concomitant Drug</td>
</tr>
<tr>
<td>Celecoxib 100-200 mg BID</td>
<td>8030</td>
<td>154 (19.2)</td>
</tr>
<tr>
<td>Ibuprofen 600-800 mg BID</td>
<td>7992</td>
<td>146 (18.5)</td>
</tr>
<tr>
<td>Naproxen 375-500 mg BID</td>
<td>7933</td>
<td>147 (18.8)</td>
</tr>
<tr>
<td>Other</td>
<td>7795 (32.5)</td>
<td>647</td>
</tr>
</tbody>
</table>

(Source: Applicant’s tables14.4.2.3.1d, 14.4.2.3.1e, and 14.4.2.3.1f from study report body)

Overall, 7785 (33%) subjects took any type of non-randomly assigned (“cross-in”) NSAID during the study: 3283 (14%) subjects before treatment discontinuation, and 5260 (22%) subjects after treatment discontinuation. Specifically, the pattern of non-randomly assigned NSAID use, types of NSAID, and number of users was similar across the three treatment groups. In each of the treatment groups, the majority of subjects used ibuprofen as an open-label choice followed by celecoxib, and then naproxen. No particular treatment group showed a predominance of use of a specific medication before or after treatment discontinuation.
• Rescue medication
Overall, 6128 (26%) subjects received rescue medication during the study. Specifically, the pattern of rescue medication use, type of rescue medications, and number of users was similar across the three treatment groups. The most commonly used rescue medications were from the opioid drug class. No particular treatment group showed a predominance of use of a specific medication before or after treatment discontinuation.

• Aspirin
Use of aspirin for CV protection was similar across treatment groups. In each of the three treatment groups, approximately 46% subjects were on aspirin for CV protection at baseline. Almost all of these subjects remained on aspirin at the End of Study (EOS) Visit. Overall, an additional 4% of subjects started aspirin during study; nearly all of them remained on aspirin at the EOS Visit.

• Gastroprotective agent
The average dose and duration of usage of esomeprazole was balanced across the treatment groups.

4.2.1.5 Primary Study Endpoint

The Agency analysis of the primary endpoint is described under the Statistical Summary section.

Below are subgroup analyses of the APTC, including exploration of cumulative drug exposure and aspirin-NSAID interaction.

4.2.1.5.1 Risk of an APTC event by cumulative drug exposure

To assess the risk of an APTC event by cumulative drug exposure (regardless of dose), the Kaplan Mayer (KM) plots for the APTC events were reviewed. The KM plots (Figure 1) do not suggest that the risk for an APTC event is cumulative in any of the products for the following reasons:
1. Within each drug, the rate of events appears similar between years 1 and 2 (and beyond). The event rates are represented by straight lines and do not accelerate with time, as it would be expected if the risk was cumulative.
2. The curves look proportional through time. There is no evidence to suggest that the hazard ratio between any two products is changing through time.
Figure 1: K-M Plot of APTC (ITT, 30 months)

The incidence rate of APTC events by each 1-year interval is presented in Table 9. The mITT population was used, as it accounts for drug exposure. There were no obvious trends of increasing incidence rates over time, for any product, which is consistent with the impression based on the K-M curves.

(Source: Figure created by the statistical review team from DBVII)
Table 9: Incidence of APTC events by 1-year interval (mITT)

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Number of events</th>
<th>Celecoxib (N= 8030)</th>
<th>Ibuprofen (N= 7990)</th>
<th>Naproxen (N= 7933)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total days of follow up</td>
<td>2.274559</td>
<td>2186964</td>
<td>2232725</td>
</tr>
<tr>
<td></td>
<td>Total PYs of follow up</td>
<td>6227.4</td>
<td>5987.6</td>
<td>6112.9</td>
</tr>
<tr>
<td></td>
<td>Incidence rate/100 PY</td>
<td>1</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>Year 2</td>
<td>Number of events</td>
<td>34</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Total days of follow up</td>
<td>1492578</td>
<td>1370397</td>
<td>1441547</td>
</tr>
<tr>
<td></td>
<td>Total PYs of follow up</td>
<td>4086.5</td>
<td>3751.9</td>
<td>3946.7</td>
</tr>
<tr>
<td></td>
<td>Incidence rate/100 PY</td>
<td>0.8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Year 3</td>
<td>Number of events</td>
<td>30</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Total days of follow up</td>
<td>1002286</td>
<td>914726</td>
<td>962073</td>
</tr>
<tr>
<td></td>
<td>Total PYs of follow up</td>
<td>2744.1</td>
<td>2504.4</td>
<td>2634.1</td>
</tr>
<tr>
<td></td>
<td>Incidence rate/100 PY</td>
<td>1</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;Year 3</td>
<td>Number of events</td>
<td>8</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Total days of follow up</td>
<td>412274</td>
<td>377172</td>
<td>394806</td>
</tr>
<tr>
<td></td>
<td>Total PYs of follow up</td>
<td>1128.7</td>
<td>1032.6</td>
<td>1080.9</td>
</tr>
<tr>
<td></td>
<td>Incidence rate/100 PY</td>
<td>0.7</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Overall</td>
<td>Incidence rate/100 PY</td>
<td>134</td>
<td>155</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>Total days of follow up</td>
<td>5181697</td>
<td>4849259</td>
<td>5031151</td>
</tr>
<tr>
<td></td>
<td>Total PYs of follow up</td>
<td>13057.9</td>
<td>12243.9</td>
<td>12693.6</td>
</tr>
<tr>
<td></td>
<td>Incidence rate/100 PY</td>
<td>1</td>
<td>1.3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

(Source: Table created by the statistical review team from DBVII)

4.2.1.5.2 Exploration of Aspirin-NSAID interaction and effect on APTC events

The use of aspirin for CV protection was similar across treatment groups. In each of the three treatment groups, approximately 46% of the subjects were on aspirin for CV protection at baseline and an additional 4% of the subjects started aspirin during study.

In consideration of the published clinical pharmacology data on aspirin drug-drug interaction with celecoxib, ibuprofen, and naproxen, the impact of the different NSAIDs used in this study on the cardioprotective effect of low-dose aspirin was evaluated. Based on the clinical pharmacology data, it was anticipated that celecoxib, a selective COX-2 inhibitor that is not expected to block acetylation of platelet COX-1 by aspirin, would not interfere with the cardioprotective effect of aspirin, compared to the propionic acid-derived NSAID inhibitors of COX-1, ibuprofen and naproxen. Based on the results presented by the Applicant (Table 10), however, no meaningful differences in the proportion of subjects with APTC event could be detected between celecoxib (2.1%) low-dose aspirin users and ibuprofen (2.2%) and naproxen (2.1%) low-dose aspirin users.
The incidence rate of APTC events among low-dose aspirin users was also similar between the treatment groups.

<table>
<thead>
<tr>
<th>Subjects taking low dose aspirin</th>
<th>Celecoxib 100-200 mg bid (N=3683)</th>
<th>Ibuprofen 600-800 mg tid (N=3695)</th>
<th>Naproxen 375-500 mg bid (N=3640)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with first APTC event, N (%)</td>
<td>77 (2.1%)</td>
<td>81 (2.2%)</td>
<td>77 (2.1%)</td>
</tr>
<tr>
<td>Median follow-up time, Years</td>
<td>1.6</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Incidence rate of first APTC event in first 100 person-years</td>
<td>1.2</td>
<td>1.3</td>
<td>1.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects not taking low dose aspirin</th>
<th>Celecoxib 100-200 mg bid (N=4347)</th>
<th>Ibuprofen 600-800 mg tid (N=4295)</th>
<th>Naproxen 375-500 mg bid (N=4293)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with first APTC event, N (%)</td>
<td>57 (1.3%)</td>
<td>74 (1.7%)</td>
<td>67 (1.6%)</td>
</tr>
<tr>
<td>Median follow-up time, Years</td>
<td>1.6</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Incidence rate of first APTC event in first 100 person-years</td>
<td>0.7</td>
<td>1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

(Source: Adapted from Applicant’s tables 14.2.1.1.5.2 and 14.2.1.1.5.4 from the Study report body 1)

Based on the Forest plot below (Figure 2), the Applicant concluded that the non-inferiority of celecoxib versus naproxen or ibuprofen is unlikely to have been confounded by the use of low-dose aspirin.
The suspected mechanism of the interaction is reversible binding of propionic acid-derived non-aspirin NSAID inhibitors of COX-1, such as naproxen or ibuprofen that competes with and prevents aspirin-mediated acetylation of platelet SER529. While platelet bound, ibuprofen and naproxen confer an antiplatelet effect. However, because they are reversibly bound (i.e., disassociate from the platelet as their serum concentration falls), it is possible that they interfere with the permanent antiplatelet effect of aspirin by leaving unacetylated platelets behind as they dissociate from their platelet binding sites. Therefore, the loss of the cardioprotective effect of aspirin would be expected to occur in the period immediately after NSAID discontinuation (the wash-out period). Additional analysis was performed by the Division of Biostatistics VII to determine if there was a difference in the proportion of subjects with first APTC event between the three treatment groups during the critical early period after study drug discontinuation. Subjects who had on-treatment APTC event and subjects with any NSAIDs use during the five-day period after study drug discontinuation were excluded from this analysis. As shown in Table 11, the number of subjects experiencing an APTC event within 5 days after study drug discontinuation was small for both non-aspirin and aspirin users, and no substantial difference between the treatment groups was observed.

(Source: Applicant’s Figure 5 from study report body, page 157)
Table 11: Number of 1st APTC events in aspirin and non-aspirin users within 5 days following treatment discontinuation (mITT)

<table>
<thead>
<tr>
<th>mITT (N)</th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
<th>Naproxen</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT, excluding subjects with on-treatment APTC and any NSAID use during the 5-day period after study drug d/c (N)</td>
<td>7140</td>
<td>7098</td>
<td>7059</td>
<td>21297</td>
</tr>
<tr>
<td>Day 1</td>
<td>23</td>
<td>22</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>aspirin</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>no aspirin</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>Day 2</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>aspirin</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>no aspirin</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Day 3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>aspirin</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>no aspirin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Day 4</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>aspirin</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>no aspirin</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Day 5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>aspirin</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>no aspirin</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

(Source: Created by Dr. Bo Li, Division of Biostatistics VII, FDA)

When interpreting the absence of a difference in the APTC results from PRECISION across the three NSAID products, it is important to note that the highest risk patients most dependent on the platelet-inactivating effect of aspirin, i.e., those who had recently experienced a CV event (MI, stroke, CABG surgery within 3 months prior to randomization), were not eligible for enrollment. Additionally, subjects were instructed to take aspirin two hours before study drug to minimize the potential for an interaction that may reduce the antiplatelet effects of aspirin; however, this intervention might only be effective for ibuprofen which has a shorter half-life than naproxen.

4.2.1.6 Secondary and Tertiary Study Endpoints

Additional outcomes of cardiovascular safety, GI, renal, and all-cause mortality outcomes were assessed as secondary or tertiary endpoints in PRECISION, and the Applicant’s results are presented in this section. As described above, the clinical events comprising these endpoints were adjudicated in accordance with pre-specified definitions performed by separate independent committees.

Despite the lack of a pre-specified hierarchical statistical testing plan, the Applicant conducted statistical testing and reported nominal confidence intervals and p-values for these outcomes. The
reported p-values are not interpretable due to multiple testing and the absence of a pre-specified testing plan. Therefore, the data from these analyses should only be interpreted descriptively.

4.2.1.6.1 Major Adverse Cardiovascular Events (MACE) Endpoint

The MACE endpoint included the APTC composite endpoint (CV-related death, non-fatal MI, and non-fatal stroke) plus coronary revascularization, or hospitalization for unstable angina or transient ischemic attack, and was analyzed as a secondary endpoint.

The time to first MACE through 30 months (ITT) and through 42 months (mITT) is presented in Table 12 and Table 13, respectively. The proportion of subjects having MACE was lowest with celecoxib (4.2% ITT, 3.1% mITT), followed by naproxen (4.3% ITT, 3.2% mITT), and then ibuprofen (4.8% ITT, 3.6% mITT). However, the differences were small, 0.1% between celecoxib and naproxen in both ITT and mITT, and 0.6% between celecoxib and ibuprofen for ITT and 0.5% for the mITT.

The proportion of subjects experiencing each component of the MACE endpoint events was also very similar across treatment groups. Small differences were detected for CV death, fatal and nonfatal MI, and revascularization, from 0.1% to 0.5%, with celecoxib having the lowest proportion of subjects for these MACE components. Almost no differences between treatment groups were detected for fatal and nonfatal stroke, hospitalization for UA and hospitalization for TIA.

<table>
<thead>
<tr>
<th>Table 12: MACE (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Celecoxib 100-200 mg bid</strong></td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Number of subjects with events (%)</td>
</tr>
<tr>
<td>MACE</td>
</tr>
<tr>
<td>CV death</td>
</tr>
<tr>
<td>Nonfatal and fatal MI</td>
</tr>
<tr>
<td>Nonfatal and fatal stroke</td>
</tr>
<tr>
<td>Hospitalization for UA</td>
</tr>
<tr>
<td>Revascularization</td>
</tr>
<tr>
<td>Hospitalization for TIA</td>
</tr>
</tbody>
</table>

(Source: Adapted from Applicant’s Table 16 from study report body, page 169)
Clinically Significant Gastrointestinal Events (CSGIE)

Clinically Significant Gastrointestinal Events (CSGIE) were defined as a composite of the following: gastroduodenal hemorrhage, gastric outlet obstruction, gastroduodenal, small bowel or large bowel perforation, large bowel hemorrhage, small bowel hemorrhage, acute GI hemorrhage of unknown origin, including presumed small bowel hemorrhage, and symptomatic gastric or duodenal ulcer.

Iron Deficiency Anemia (IDA) was defined as clinically significant iron deficiency anemia of GI origin or decrease in Hct and/or Hgb (defined as Hct ≥10 points and or Hgb of ≥2g/dl from baseline).

The adjudicated GI endpoints for the ITT and mITT population are presented in Table 14. For the ITT, the proportion of subjects having CSGIE was similar between groups: 0.7% for celecoxib and naproxen, and 0.9% for ibuprofen. The proportion of subjects having IDA of GI origin was higher in the naproxen and ibuprofen groups compared to the celecoxib group: 0.4% for celecoxib, 0.8% for ibuprofen, and 0.9% for naproxen. For the mITT, the proportion of subjects having CSGIE was greater in the ibuprofen and naproxen groups compared to the celecoxib group: 0.3% for celecoxib, 0.7% for ibuprofen, and 0.7% for naproxen. Similar results were found for the IDA of GI origin: 0.3% for celecoxib, 0.7% for ibuprofen, and 0.8% for naproxen.

### Table 13: MACE (mITT)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 100-200 mg</th>
<th>Ibuprofen 600-800 mg</th>
<th>Naproxen 375-500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>bid</td>
<td>tid</td>
<td>bid</td>
</tr>
<tr>
<td>N</td>
<td>8,030</td>
<td>7,990</td>
<td>7,933</td>
</tr>
<tr>
<td>Number of Subjects with Events (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>247 (3.1%)</td>
<td>284 (3.6%)</td>
<td>253 (3.2%)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>35 (0.4%)</td>
<td>51 (0.6%)</td>
<td>49 (0.6%)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>58 (0.7%)</td>
<td>76 (1.0%)</td>
<td>53 (0.7%)</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>43 (0.5%)</td>
<td>32 (0.4%)</td>
<td>45 (0.6%)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>132 (1.6%)</td>
<td>158 (2.0%)</td>
<td>122 (1.5%)</td>
</tr>
<tr>
<td>Hospitalization for TIA</td>
<td>12 (0.1%)</td>
<td>21 (0.3%)</td>
<td>16 (0.2%)</td>
</tr>
</tbody>
</table>

(Source: Adapted from Table 7 from the proposed product label)
### Table 14: Adjudicated gastrointestinal events

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th></th>
<th>mITT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celecoxib 100-200 mg bid N=8072</td>
<td>Ibuprofen 600-800 mg tid N=8040</td>
<td>Naproxen 375-500 mg bid N=7969</td>
</tr>
<tr>
<td>Number of subjects with events (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSGIE</td>
<td>55 (0.7%)</td>
<td>72 (0.9%)</td>
<td>56 (0.7%)</td>
</tr>
<tr>
<td>IDA of GI origin</td>
<td>33 (0.4%)</td>
<td>64 (0.8%)</td>
<td>69 (0.9%)</td>
</tr>
</tbody>
</table>

4.2.1.6.3 Clinically significant cardiovascular and renal events

The Applicant grouped together and analyzed clinically significant renal events, hospitalization for heart failure, or hospitalization for hypertension as a composite endpoint.

Clinically significant renal events were adjudicated in a blinded fashion by a Clinical Events Committee and were defined as:

1. Verified serum creatinine level of ≥2.0 mg/dL (i.e., the persistence of serum creatinine elevation ≥24 hours following the initial acute serum creatinine elevation), and an increase of verified serum creatinine level of ≥0.7 mg/dL from baseline.
2. Hospitalization for acute renal failure defined as:
   a. Doubling of the baseline serum creatinine, or
   b. Hyperkalemia (defined as >6 mmol/dL) with ≥50% elevation in serum creatinine (hyperkalemia needs to be confirmed to rule out false elevation related to hemolysis).
3. Initiation of hemodialysis or peritoneal dialysis.

The event rates were low overall. As illustrated in Table 15, the proportion of subjects experiencing clinically significant renal events or hospitalization for heart failure or hypertension was numerically lower in the celecoxib group compared with the ibuprofen and naproxen groups.

(Source: Adapted from Applicant’s Table 21 and Table 22 from study report body, pp 184-185)
**Table 15: Clinically significant renal events or hospitalization for CHF or hypertension**

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>mITT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celecoxib 100-200 mg bid</td>
<td>Ibuprofen 600-800 mg tid</td>
</tr>
<tr>
<td></td>
<td>N=8072</td>
<td>N=8040</td>
</tr>
<tr>
<td>Number of subjects with events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS Renal Events</td>
<td>57 (0.7%)</td>
<td>92 (1.1%)</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>45 (0.6%)</td>
<td>46 (0.6%)</td>
</tr>
<tr>
<td>Hospitalization for HTN</td>
<td>24 (0.3%)</td>
<td>40 (0.5%)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>118 (1.5%)</td>
<td>166 (2.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Celecoxib 100-200 mg bid</td>
<td>Ibuprofen 600-800 mg tid</td>
</tr>
<tr>
<td></td>
<td>N=8030</td>
<td>N=7990</td>
</tr>
<tr>
<td>Number of subjects with events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS Renal Events</td>
<td>42 (0.5%)</td>
<td>73 (0.9%)</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>28 (0.3%)</td>
<td>38 (0.5%)</td>
</tr>
<tr>
<td>Hospitalization for HTN</td>
<td>25 (0.3%)</td>
<td>37 (0.5%)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>89 (1.1%)</td>
<td>139 (1.7%)</td>
</tr>
</tbody>
</table>

(Source: Adapted from Applicant’s Table 25 and Table 26 from study report body, page 190-191)

DAAAP requested input from the Division of Cardiovascular and Renal Products (DCRP) for the appropriateness of the definition used for clinically significant renal events, and whether it is clinically logical to group “clinically significant” renal events, hospitalization for CHF, or hospitalization for hypertension into one composite endpoint.

DCRP reviewer, Dr. Kimberly Smith, responded to the DAAAP’s question as follow:

“The applicant’s definition of “clinically significant renal events” is not standard. It seems that the applicant intended to capture acute kidney injury events based on references to “the initial acute serum creatinine elevation” and “acute renal failure” in the definition; however, given the references to changes from baseline, the definition could also capture cases of chronic progression. Similarly, dialysis can be acute or chronic. It is not clear what the basis is for this definition or how sensitive or specific it would be for clinically meaningful cases of acute kidney injury, if that was the intent.

It is not clear why the applicant chose to group renal events, hospitalization for heart failure, and hospitalization for hypertension into a composite endpoint. It may make sense if they were trying to capture key safety events that are not necessarily related but are uncommon and therefore not likely to occur at a frequency high enough to draw meaningful conclusions regarding the individual components. Grouping these events in this way does not improve our understanding of the renal safety of celecoxib relative to the other interventions that were tested.”
4.2.1.6.4** All-cause mortality**

Death from any cause was analyzed as one component of the tertiary composite endpoint: all-cause mortality, non-fatal stroke, or non-fatal MI.

In the ITT population there were 132 (1.6%), 163 (2.0%) and 142 (1.8%) deaths in the celecoxib, naproxen and ibuprofen groups, respectively. In the mITT populations celecoxib, naproxen and ibuprofen were associated with 53 (0.7%), 79 (1.0%), and 73 (0.9%) deaths, respectively (Table 16).

**Table 16: Death (All-cause)**

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>mITT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celecoxib 100-200 mg bid N=8072</td>
<td>Ibuprofen 600-800 mg tid N=8040</td>
</tr>
<tr>
<td>Number of subjects with events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death of any cause</td>
<td>132 (1.6%)</td>
<td>142 (1.8%)</td>
</tr>
</tbody>
</table>

|                | Celecoxib 100-200 mg bid N=8030   | Ibuprofen 600-800 mg tid N=7990   | Naproxen 375-500 mg bid N=7933   |
| Number of subjects with events (%) |                          |                                   |
| Death of any cause       | 53 (0.7%)                         | 73 (0.9%)                         | 79 (1%)                          |

(Source: Applicant’s Table 18 and Table 19 from study report body, page 181)

For further analyses on deaths (all-cause), refer to the General Safety section.

4.2.1.7 **General Safety**

The overall safety profile of the study drugs was consistent with previously reported studies, with no newly identified safety findings.

4.2.1.7.1 **Deaths**

The ITT, mITT, and the safety populations each has a different total number of patient deaths due to the way the cohort was defined. The reader is encouraged to closely examine the cohort being described in the tables below when considering the results.

Six hundred and ten (610) deaths were collected via the End of Treatment (EOT) and End of Study (EOS) Case Report Form (CRF) pages (CRF dataset). Six hundred and twenty-one (621) deaths were collected via the endpoint/AE CRF pages and reported throughout the study to the independent endpoint adjudication committee (adjudicated dataset).

Among these two datasets, there was an overlap of 607 deaths in both CRF and adjudicated datasets:
• Three (3) deaths existed in the CRF dataset but not the adjudicated dataset. These deaths took place after end of study and were NOT supposed to be recorded in the clinical database, per protocol.

• Fourteen (14) deaths existed in the adjudicated dataset but not in the CRF dataset; all 14 deaths are recorded in the clinical database via endpoint/AE CRF pages, and not via EOT or EOS pages. Therefore, they were not included in the CRF dataset.

Public records were used to follow-up the vital status of subjects after study withdrawal. Deaths that occurred during double-blind (DB) treatment and follow-up period are summarized for the safety population in Table 17 below. The safety population consisted of all randomized subjects who received at least one dose of study drug. The DB period was defined by the Applicant to include the first 30-days post-treatment, and the follow-up period was the time off treatment after these 30 days. However, to better understand the occurrence of death in relation to the time of study drug discontinuation, the tables that follow present deaths by three time-periods; double-blind (not including the 30 days following study drug discontinuation), 30-day follow-up (the 30 days of follow-up after study drug was discontinued), and follow-up (excluding the 30 days after the study drug was discontinued).

<table>
<thead>
<tr>
<th>Table 17: Deaths identified in CRF dataset- incidence rate per 100 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Celecoxib 100-200 mg bid</strong></td>
</tr>
<tr>
<td>N=8030</td>
</tr>
<tr>
<td>DB 30 days following study drug d/c 1st 30 days N (rate per 100</td>
</tr>
<tr>
<td>F/U 1st 30 days N (rate per 100 person-years)</td>
</tr>
<tr>
<td><strong>Ibuprofen 600-800 mg tdd</strong></td>
</tr>
<tr>
<td>N=7992</td>
</tr>
<tr>
<td>DB 30 days following study drug d/c 1st 30 days N (rate per 100</td>
</tr>
<tr>
<td>F/U 1st 30 days N (rate per 100 person-years)</td>
</tr>
<tr>
<td><strong>Naproxen 375-500 mg bid</strong></td>
</tr>
<tr>
<td>N=7933</td>
</tr>
<tr>
<td>DB 30 days following study drug d/c 1st 30 days N (rate per 100</td>
</tr>
<tr>
<td>F/U 1st 30 days N (rate per 100 person-years)</td>
</tr>
</tbody>
</table>

The incidence rate of deaths during the 30 days following study drug discontinuation was substantially higher as compared to the incidence rate of deaths during the double-blind treatment or later in the follow-up period for all three groups (Table 17).

As expected, more deaths occurred in the RA compared to the OA patient population for all treatment groups (refer to Table 18a and 18b). Among patients with OA, the proportion of subjects who died from all-causes was similar between treatment groups. However, the proportion of RA subjects who died from all-causes was the highest in the naproxen group, followed by the ibuprofen, and then the celecoxib group (for the ITT: 3.8%, 2.2%, and 1.9%, respectively and for the mITT: 2.4%, 1.5%, and 0.4%, respectively). These results were driven particularly by the difference in the non-CV death; in the ITT: naproxen (2.4%), followed by ibuprofen (1%), and celecoxib (0.7%) and in the mITT: naproxen (1.4%), followed by ibuprofen (0.2%), and celecoxib (0.1%). In the mITT analysis (Tables 17 and 18), between-group imbalance for the RA population was also noted for the CV death. Celecoxib had the lowest proportion of CV death (0.3%), followed by naproxen (1%), and then ibuprofen (1.2%).
### Table 18a: Adjudicated deaths by arthritis type (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 100-200 mg bid</th>
<th>Ibuprofen 600-800 mg tid</th>
<th>Naproxen 375-500 mg bid</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=8072</td>
<td>N=8040</td>
<td>N=7969</td>
<td>N=24081</td>
</tr>
<tr>
<td>Deaths, %</td>
<td>132 (1.6%)</td>
<td>142 (1.8%)</td>
<td>163 (2%)</td>
<td>437 (1.8%)</td>
</tr>
<tr>
<td>CV Deaths, %</td>
<td>68 (0.8%)</td>
<td>80 (1%)</td>
<td>86 (1%)</td>
<td>234 (1%)</td>
</tr>
<tr>
<td>Non-CV Deaths, %</td>
<td>64 (0.8%)</td>
<td>62 (0.8%)</td>
<td>77 (1%)</td>
<td>203 (0.8%)</td>
</tr>
</tbody>
</table>

**RA Subjects**

<table>
<thead>
<tr>
<th></th>
<th>813</th>
<th>832</th>
<th>791</th>
<th>2436</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, %</td>
<td>15 (1.9%)</td>
<td>18 (2.2%)</td>
<td>30 (3.8%)</td>
<td>63 (2.6%)</td>
</tr>
<tr>
<td>CV Deaths, %</td>
<td>9 (1.1%)</td>
<td>10 (1.2%)</td>
<td>11 (1.4%)</td>
<td>30 (1.2%)</td>
</tr>
<tr>
<td>Non-CV Deaths, %</td>
<td>6 (0.7%)</td>
<td>8 (1%)</td>
<td>19 (2.4%)</td>
<td>33 (1.4%)</td>
</tr>
</tbody>
</table>

**OA Subjects**

<table>
<thead>
<tr>
<th></th>
<th>7259</th>
<th>7208</th>
<th>7178</th>
<th>21645</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, %</td>
<td>117 (1.6%)</td>
<td>124 (1.7%)</td>
<td>133 (1.9%)</td>
<td>374 (1.7%)</td>
</tr>
<tr>
<td>CV Deaths, %</td>
<td>59 (0.8%)</td>
<td>70 (1%)</td>
<td>75 (1%)</td>
<td>204 (0.9%)</td>
</tr>
<tr>
<td>Non-CV Deaths, %</td>
<td>58 (0.8%)</td>
<td>54 (0.8%)</td>
<td>58 (0.8%)</td>
<td>170 (0.8%)</td>
</tr>
</tbody>
</table>

**Note:** Data Source 1: Adjudicated dataset (all randomized subjects), including only adjudicated deaths by 30 months after randomization.
(Source: Adapted from Applicant’s Table 14.1.1.1.1.5 from study report body, page 228)

### Table 18b: Adjudicated deaths by arthritis type (mITT)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 100-200 mg bid</th>
<th>Ibuprofen 600-800 mg tid</th>
<th>Naproxen 375-500 mg bid</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=8030</td>
<td>N=7990</td>
<td>N=7933</td>
<td>N=23953</td>
</tr>
<tr>
<td>Deaths, %</td>
<td>53 (0.7%)</td>
<td>73 (0.9%)</td>
<td>79 (1%)</td>
<td>205 (0.9%)</td>
</tr>
<tr>
<td>CV Deaths, %</td>
<td>35 (0.4%)</td>
<td>51 (0.6%)</td>
<td>49 (0.6%)</td>
<td>135 (0.6%)</td>
</tr>
<tr>
<td>Non-CV Deaths, %</td>
<td>18 (0.2%)</td>
<td>22 (0.3%)</td>
<td>30 (0.4%)</td>
<td>70 (0.3%)</td>
</tr>
</tbody>
</table>

**RA Subjects**

<table>
<thead>
<tr>
<th></th>
<th>810</th>
<th>828</th>
<th>787</th>
<th>2425</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, %</td>
<td>3 (0.4%)</td>
<td>12 (1.5%)</td>
<td>19 (2.4%)</td>
<td>34 (1.4%)</td>
</tr>
<tr>
<td>CV Deaths, %</td>
<td>2 (0.3%)</td>
<td>10 (1.2%)</td>
<td>8 (1%)</td>
<td>20 (0.8%)</td>
</tr>
<tr>
<td>Non-CV Deaths, %</td>
<td>1 (0.1%)</td>
<td>2 (0.2%)</td>
<td>11 (1.4%)</td>
<td>14 (0.6%)</td>
</tr>
</tbody>
</table>

**OA Subjects**

<table>
<thead>
<tr>
<th></th>
<th>7220</th>
<th>7162</th>
<th>7146</th>
<th>21528</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, %</td>
<td>50 (0.7%)</td>
<td>61 (0.9%)</td>
<td>60 (0.8%)</td>
<td>171 (0.8%)</td>
</tr>
<tr>
<td>CV Deaths, %</td>
<td>33 (0.5%)</td>
<td>41 (0.6%)</td>
<td>41 (0.6%)</td>
<td>115 (0.5%)</td>
</tr>
<tr>
<td>Non-CV Deaths, %</td>
<td>17 (0.2%)</td>
<td>20 (0.3%)</td>
<td>19 (0.3%)</td>
<td>56 (0.3%)</td>
</tr>
</tbody>
</table>

(Source: Adapted from Applicant’s Table 14.1.1.1.1.5 from study report body, page 228)

Further examination of all adjudicated deaths among RA subjects collected throughout the entire duration of PRECISION, identified 25 non-CV deaths for the naproxen group, 12 for the
ibuprofen group, and eight for the celecoxib group (Table 19). Among the 25 subjects in the naproxen group, seven subjects had events in the “Neoplasms benign, malignant and unspecified (including cysts and polyps)” System Organ Class (SOC), and eight subjects had events in the “Infections and infestations” SOC. No other specific pattern was observed.

Table 19: Non-cardiovascular deaths in RA subjects collected throughout the entire duration of the study

<table>
<thead>
<tr>
<th>SOC Group</th>
<th>Naproxen 375-500 mg bid</th>
<th>Ibuprofen 600-800 mg tid</th>
<th>Celecoxib 100-200 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>25</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td>7</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Data Source 1: Adjudicated dataset (all randomized subjects), including all adjudicated deaths collected throughout the entire duration of PRECISION.
(Source: Applicant’s Table 20 from study report body, page 182)

Neoplasms and infections are common in RA patients receiving disease modifying therapies. To further assess the numerical imbalance between treatment groups for non-cardiovascular deaths in RA patients, the Applicant was asked to provide the number of patients for each treatment group that was taking disease modifying anti-rheumatic drugs (DMARDs) at the time of the event of death.

In a response submitted in November 2017, the Applicant described that of the 45 RA patients who died of non-CV related causes (Table 20), 36 (4 in celecoxib, 10 in ibuprofen, 22 in naproxen) had concomitant use of DMARDs during the study period; 28 (4 in celecoxib, 8 in ibuprofen, 16 in naproxen) died while taking a DMARD during the treatment period. Of the 45 patients, 39 (4 in celecoxib, 12 in ibuprofen, 23 in naproxen) used a DMARD during the study period, irrespective of concomitant status with the study drug; 30 (4 in celecoxib, 9 in ibuprofen, 17 in naproxen) died while taking a DMARD.
Table 20: Non-cardiovascular death in RA subjects by DMARD use

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
<th>Naproxen</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CV deaths in RA</td>
<td>8</td>
<td>12</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Used DMARDs during</td>
<td>4</td>
<td>10</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Died while taking</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>DMARD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on this additional information provided, the imbalance of DMARD use between treatment groups explains the numerical imbalance for non-CV deaths among RA subjects presented in Table 18a and 18b. A higher proportion of subjects from the naproxen group received a DMARD during the study and died while taking the DMARD, primarily due to infections and neoplasms, compared to the celecoxib and ibuprofen groups.

4.2.1.7.2 Serious Adverse Events (SAE)

Overall, 1,481 (18%), 1,637 (21%), 1,622 (20%) subjects experiencing an SAE were reported for the celecoxib group, ibuprofen group, and naproxen group, respectively. All SAEs by SOC and preferred term for the most frequently reported events and for events of interest are summarized for the safety population in Table 21.
The most frequently reported SAEs by SOC were within the Cardiac, Nervous system, and Gastrointestinal Disorders. Overall, the incidence of SAEs in those SOC categories was lower for the celecoxib group compared to the ibuprofen and naproxen groups, but the differences were very small. The highest difference was between celecoxib and ibuprofen (0.9%) for the Cardiac Disorders SOC (celecoxib: 275 [3.4%]; ibuprofen: 343 [4.3%]; naproxen: 313 [3.9%]). The proportion of patients with a SAE for the following preferred terms, chest pain, MI, HTN, renal failure, gastric ulcer, and anemia (all with ≤ 1% incidence rate), was also slightly lower for the celecoxib group compared with the ibuprofen and naproxen groups. In the context of interpreting...
the safety results in this study, it is important to reiterate that the low dose range of celecoxib is being compared to a higher dose range of ibuprofen and naproxen for adverse events that are known to be dose-dependent.

4.2.1.7.3 Adverse Events Leading to Study Drug Discontinuation

Overall, treatment-emergent adverse events (TEAEs) that were observed in ≥1% of subjects in any treatment group leading to treatment discontinuation were comparable between the three groups, except for HTN and blood creatinine increased, for which fewer patients from the celecoxib group discontinued treatment compared to ibuprofen and naproxen (Table 22).

Table 22: Discontinuations due to adverse events occurring in ≥ 1% of subjects (safety population)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 100-200 mg bid N=8030</th>
<th>Ibuprofen 600-800 mg tid N=7992</th>
<th>Naproxen 375-500 mg bid N=7933</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs by PT leading to treatment discontinuation in ≥1% subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HTN</td>
<td>78 (1%)</td>
<td>140 (1.8%)</td>
<td>106 (1.3%)</td>
</tr>
<tr>
<td>- Blood creatinine increased</td>
<td>54 (0.7%)</td>
<td>105 (1.3%)</td>
<td>49 (0.6%)</td>
</tr>
</tbody>
</table>

Note: The numbers in this table do not reflect the reclassification. Discontinuations due to AE from treatment and from study, reflecting the reclassification, are described in Table 1.
(Source: Adapted from Applicant’s Table 14.3.1.1.2.4 from Study report body 2, page 12424)

4.2.1.7.4 Common Adverse Events

A total of 23,955 subjects (safety population) were treated during the study and were included in the analysis of AEs. Overall, 19,742 (82.4%) subjects experienced at least one TEAE (Table 23). A similar proportion of subjects (approximately 82%) experienced TEAEs in each of the three treatment groups. Also, a similar proportion of subjects in each of the three treatment groups experienced AEs rated by the investigator as severe (approximately 21%) or SAE (approximately 19.7%).

Table 23: Treatment-emergent adverse events (safety population)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 100-200 mg bid</th>
<th>Ibuprofen 600-800 mg tid</th>
<th>Naproxen 375-500 mg bid</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects evaluable for AEs</td>
<td>8030</td>
<td>7992</td>
<td>7933</td>
<td>23955</td>
</tr>
<tr>
<td>Number of AEs</td>
<td>32810</td>
<td>34060</td>
<td>33669</td>
<td>100539</td>
</tr>
<tr>
<td>Subjects with AEs</td>
<td>6542 (81.5)</td>
<td>6669 (83.4)</td>
<td>6531 (82.3)</td>
<td>19742 (82.4)</td>
</tr>
<tr>
<td>Subjects with SAEs</td>
<td>1473 (18.3)</td>
<td>1624 (20.3)</td>
<td>1611 (20.3)</td>
<td>4708 (19.7)</td>
</tr>
<tr>
<td>Subjects with severe AEs</td>
<td>1589 (19.8)</td>
<td>1724 (21.6)</td>
<td>1710 (21.6)</td>
<td>5023 (21.0)</td>
</tr>
</tbody>
</table>

(Source: Applicant’s Table 27 from study report, page 196)

Time to onset for TEAEs was between 0 and 6 months from study start for the majority of events (82% subjects with AE). Over time, a decreasing proportion of subjects experienced a TEAE, 6 to 12 months: 60%, 12 to 18 months: 50%, 18-24 months: 47%, 24 to 30 months: 45%, 30 to 36 months: 44%, and 36 to 42 months: 36%. This decline is likely related to the patients remaining in the study being able to tolerate the medication (i.e., depletion of susceptibles).

TEAEs occurring in ≥5% of subjects are presented in Table 24.

The most frequently reported TEAEs by preferred term (PT) were as follows:

- **Osteoarthritis** - celecoxib group: 14% of subjects, ibuprofen group: 13%, naproxen group: 13%.
- **Hypertension** - celecoxib group: 10% of subjects, ibuprofen group: 13%, naproxen group: 11%.
- **Arthralgia** - celecoxib group: 10%, ibuprofen group: 9%, and naproxen group: 10%.
Table 24: Treatment-emergent adverse events by SOC and PT occurring in ≥5% of subjects (safety population)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Celecoxib 100-200 mg BID</th>
<th>Ibuprofen 600-800 mg TID</th>
<th>Naproxen 375-500 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>221 (2.8)</td>
<td>437 (5.5)</td>
<td>331 (4.2)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>275 (3.4)</td>
<td>347 (4.3)</td>
<td>409 (5.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>642 (8.0)</td>
<td>545 (6.8)</td>
<td>569 (7.2)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>393 (4.9)</td>
<td>424 (5.3)</td>
<td>436 (5.5)</td>
</tr>
<tr>
<td>Gastrooesophageal reflux disease</td>
<td>402 (5.0)</td>
<td>407 (5.1)</td>
<td>389 (4.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>430 (5.4)</td>
<td>484 (6.1)</td>
<td>508 (6.4)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>1497 (18.6)</td>
<td>1560 (19.5)</td>
<td>1477 (18.6)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>471 (5.9)</td>
<td>483 (6.0)</td>
<td>441 (5.6)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>373 (4.6)</td>
<td>426 (5.3)</td>
<td>375 (4.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>586 (7.3)</td>
<td>596 (7.5)</td>
<td>561 (7.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>427 (5.3)</td>
<td>467 (5.8)</td>
<td>430 (5.4)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>2273 (28.3)</td>
<td>2114 (26.5)</td>
<td>2190 (27.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>793 (9.9)</td>
<td>679 (8.5)</td>
<td>788 (9.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>553 (6.9)</td>
<td>526 (6.6)</td>
<td>558 (7.0)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1102 (13.7)</td>
<td>1011 (12.7)</td>
<td>1007 (12.7)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>456 (5.7)</td>
<td>426 (5.3)</td>
<td>423 (5.3)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>364 (4.5)</td>
<td>415 (5.2)</td>
<td>365 (4.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>364 (4.5)</td>
<td>415 (5.2)</td>
<td>365 (4.6)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>776 (9.7)</td>
<td>1039 (13.0)</td>
<td>871 (11.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>776 (9.7)</td>
<td>1039 (13.0)</td>
<td>871 (11.0)</td>
</tr>
</tbody>
</table>

(Source: Applicant’s Table 28 from study report, page 197)
The proportion of subjects with TEAE was generally comparable among the treatment groups. However, the proportion of subjects with hypertension (HTN), blood pressure increased, anemia, iron-deficiency anemia, hemoglobin decreased, renal failure, and blood creatinine increased was lower in the celecoxib group compared with the ibuprofen and naproxen groups. These data should be interpreted in the context of low dose celecoxib being compared to relatively higher doses of ibuprofen and naproxen.

- **Hypertension** – celecoxib group: 10%, ibuprofen group: 13%, naproxen group: 11%.
- Blood pressure increased: celecoxib group: 2.3%, ibuprofen group: 3.1%, and naproxen group: 2.5%.
- **Anemia** - celecoxib group: 3%, ibuprofen group: 6%, and naproxen group: 4%.
- Iron-deficiency anemia: celecoxib group: 0.7%, ibuprofen group: 1.6%, and naproxen group: 1.7%.
- Hemoglobin decreased: celecoxib group: 0.9%, ibuprofen group: 1.8%, and naproxen group: 1.6%.
- Renal failure: celecoxib group: 0.6%, ibuprofen group: 1.4%, and naproxen group: 1%.
- Blood creatinine increased: 1.8%, ibuprofen group: 3.4%, and naproxen group: 1.9%.

Adverse events with the biggest difference between treatment groups (1% to 3%) were HTN and anemia, with ibuprofen having the highest proportion of subjects experiencing those events. At the same time, ibuprofen had the lowest proportion of subjects experiencing the AE of arthralgia. Also, fewer patients from the ibuprofen and naproxen groups discontinued treatment due to insufficient clinical response. These data can potentially be explained by the fact that higher doses worked better to treat the pain of arthritis but resulted in higher incidences of NSAID class-related AEs. However, without having data on comparable doses for the three treatment groups in this study, this statement remains speculative.

### 4.2.1.7.5 Clinical Laboratory Evaluations

**Laboratory Values over Time**

Laboratory abnormalities during the study for subjects who had normal baseline values were observed in 41%, 43%, and 44% subjects in the celecoxib group, naproxen group, and ibuprofen group, respectively (Table 25). The most frequently reported laboratory abnormalities (reported by ≥2% subjects in any group) are presented in Table 23. The number of subjects with these abnormalities was similar among the three treatment groups. The most frequently reported abnormalities were >1.25 × ULN in CRP (high sensitivity) levels and >1.3 × ULN in RF. The frequency of BUN and creatinine abnormalities (>1.3 × ULN) was smaller in the celecoxib group compared with the naproxen and ibuprofen groups. The number of subjects with ALT, AST, and HbA1c abnormalities was similar among the three treatment groups.
Table 25: Laboratory test abnormalities for subjects with normal baseline values occurring in ≥ 2% subjects (safety population)

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter and Units</th>
<th>Celecoxib 100-200 mg bid</th>
<th>Ibuprofen 600-800 mg tid</th>
<th>Naproxen 375-500 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N (18)</td>
<td>N (18)</td>
<td>N (18)</td>
</tr>
<tr>
<td>Hematology</td>
<td>Lymphocytes (Absolute) 10^3/mm³</td>
<td>7400 (171 (2.3))</td>
<td>7377 (187 (2.5))</td>
<td>7305 (181 (2.5))</td>
</tr>
<tr>
<td></td>
<td>Total Neutrophils (Absolute) 10^3/mm³</td>
<td>7113 (209 (2.9))</td>
<td>7101 (210 (3.0))</td>
<td>7011 (160 (2.3))</td>
</tr>
<tr>
<td></td>
<td>Eosinophils (Absolute) 10^3/mm³</td>
<td>7113 (290 (4.1))</td>
<td>7101 (325 (4.5))</td>
<td>7011 (330 (4.7))</td>
</tr>
<tr>
<td></td>
<td>Monocytes (Absolute) 10^3/mm³</td>
<td>7520 (287 (3.8))</td>
<td>7522 (332 (4.4))</td>
<td>7423 (425 (5.7))</td>
</tr>
<tr>
<td>Renal function</td>
<td>Blood Urea Nitrogen mg/dL</td>
<td>6181 (469 (7.6))</td>
<td>6158 (746 (12.1))</td>
<td>6029 (634 (10.5))</td>
</tr>
<tr>
<td></td>
<td>Creatinine mg/dL</td>
<td>6894 (137 (2.0))</td>
<td>6955 (281 (4.0))</td>
<td>6896 (163 (2.4))</td>
</tr>
<tr>
<td>Lipids</td>
<td>HDL Cholesterol mg/dL</td>
<td>4111 (82 (2.0))</td>
<td>4007 (86 (2.1))</td>
<td>4108 (73 (1.8))</td>
</tr>
<tr>
<td></td>
<td>Triglycerides mg/dL</td>
<td>3248 (378 (11.6))</td>
<td>3203 (426 (13.3))</td>
<td>3276 (387 (11.8))</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Potassium meq/L</td>
<td>7189 (90 (1.3))</td>
<td>7157 (184 (2.6))</td>
<td>7085 (78 (1.1))</td>
</tr>
<tr>
<td></td>
<td>Bicarbonate (venous) meq/L</td>
<td>7534 (225 (3.0))</td>
<td>7524 (322 (4.3))</td>
<td>7448 (246 (3.3))</td>
</tr>
<tr>
<td>Clinical Chemistry (Other)</td>
<td>Glucose mg/dL</td>
<td>4819 (221 (4.6))</td>
<td>4796 (169 (3.5))</td>
<td>4851 (180 (3.7))</td>
</tr>
<tr>
<td></td>
<td>Glycosylated Hemoglobin (HbA1c) %</td>
<td>610 (99 (16.2))</td>
<td>587 (103 (17.5))</td>
<td>531 (87 (16.4))</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid Factor IU/mL</td>
<td>211 (94 (44.5))</td>
<td>222 (95 (42.8))</td>
<td>212 (102 (48.1))</td>
</tr>
<tr>
<td></td>
<td>CRP (High Sensitivity) mg/L</td>
<td>1953 (1070 (54.8))</td>
<td>1876 (924 (49.3))</td>
<td>1932 (1640 (53.8))</td>
</tr>
</tbody>
</table>

(Source: Applicant’s Table 33 from study report, page 212)

**Median Change from Baseline**

In general, the median changes from baseline were minor for most parameters. Mean Hgb and Hct showed minor decreases from baseline, and these were smaller in the celecoxib group compared with the naproxen or ibuprofen groups. Figure 3 illustrates the mean change from baseline for hematocrit.
Figure 3: Mean change from baseline for hematocrit at each visit (safety population)

(Source: Applicant’s Figure 14.3.3.4 from study report body 11, page 71)

4.2.1.7.6 Blood Pressure – Full PRECISION Safety Population
Small increases from baseline in sitting systolic and diastolic BP were observed early in the study; the increases in systolic BP persisted throughout the study. These changes were smaller in magnitude for the celecoxib group compared with the other treatment groups.

The mean changes from baseline for systolic and diastolic BP are presented in Figure 4 and 5, respectively, showing that a lesser net increase was observed for the celecoxib group compared with the other treatment groups.
Figure 4: Mean changes from baseline in systolic BP (safety population)

(Source: Applicant’s Figure 22 from study report body 1, page 216)
Most subjects had SBP<140 mmHg and DBP<90 mmHg at the outset of the study (Table 26). The proportion of subjects with SBP <140 mmHg and DBP <90 mmHg decreased by 9% or more for all three treatment groups (10% in the celecoxib group, 14% in the ibuprofen group, and 11% in the naproxen group) at Month 1 compared with baseline, and then remained similar through the end of study.

Table 26: Subjects with BP < 140/90 mm Hg (safety population)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib 100-200 mg bid N=8030</th>
<th>Ibuprofen 600-800 mg tid N=7992</th>
<th>Naproxen 375-500 mg bid N=7933</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, n</td>
<td>N=8030</td>
<td>N=7992</td>
<td>N=7992</td>
</tr>
<tr>
<td>SBP&lt;140 mmHg and DBP&lt;90 mmHg</td>
<td>7598 (95%)</td>
<td>7583 (95%)</td>
<td>7528 (95%)</td>
</tr>
<tr>
<td>Month 1, n</td>
<td>N=7289</td>
<td>N=7241</td>
<td>N=7246</td>
</tr>
<tr>
<td>SBP&lt;140 mmHg and DBP&lt;90 mmHg</td>
<td>6187 (85%)</td>
<td>5828 (81%)</td>
<td>6066 (84%)</td>
</tr>
<tr>
<td>End of study, n</td>
<td>N=2959</td>
<td>N=2738</td>
<td>N=2856</td>
</tr>
<tr>
<td>SBP&lt;140 mmHg and DBP&lt;90 mmHg</td>
<td>2474 (84%)</td>
<td>2178 (80%)</td>
<td>2361 (83%)</td>
</tr>
</tbody>
</table>

(Source: Adapted from Applicant’s Table 14.3.4.2.8 from study report body 11, page 64)
Increases of ≥30 mmHg from baseline in sitting SBP were observed in 869 subjects (11%) in the celecoxib group, 1211 subjects (16%) in the ibuprofen group, and 1028 subjects (13%) in the naproxen group. Increases of ≥20 mmHg from baseline in sitting DBP were observed in 563 subjects (7%) in the celecoxib group, 639 subjects (8%) in the ibuprofen group, and 626 subjects (8%) in the naproxen group.

4.2.2 ABPM substudy

4.2.2.1 Disposition of subjects
Of the 589 subjects who were screened, 546 were enrolled (had a valid baseline ABP measure), and 444 were included in the mITT population by virtue of being randomized to treatment and having a baseline and at least one post-baseline ABPM assessment during the course of the study (Table 27). All 444 subjects were included in the Month 4 analysis; a total of 374 of 444 subjects completed 4 months of the substudy with valid ABPM assessments, whereas the remaining 70 patients (20 celecoxib, 33 ibuprofen, and 17 naproxen) did not have a valid Month 4 ABPM assessment. For those 70 patients, the Month 2 assessment was used at Month 4. Four hundred and thirteen patients had valid baseline and Month 2 ABPM assessments. All mITT patients received study drug, and mean daily dose for the mITT patients was mean(SD): 208(34) mg, 2030(236) mg, and 851.38(98) mg for celecoxib, ibuprofen and naproxen, respectively.

Table 27: Subject disposition – ABPM substudy

<table>
<thead>
<tr>
<th>Celecoxib 100-200 mg BID</th>
<th>Ibuprofen 600-800 mg TID</th>
<th>Naproxen 375-500 mg BID</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened 589</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolled 546</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In mITT Population</td>
<td>146</td>
<td>151</td>
<td>147</td>
</tr>
<tr>
<td>With Month 2 Data</td>
<td>134 (91.78)</td>
<td>142 (94.04)</td>
<td>137 (93.20)</td>
</tr>
<tr>
<td>With Month 4 Data</td>
<td>126 (86.30)</td>
<td>118 (78.15)</td>
<td>130 (88.44)</td>
</tr>
</tbody>
</table>

(Source: Applicant’s Table 14.1.1.1.1 from study report, page 69)

4.2.2.2 Subjects baseline characteristics
The majority of patients had a primary diagnosis of OA (92%). The mean age of the ABPM subjects was 62 years, 80% were Caucasian, and 54% were female. The average weight was 92 kg and average BMI was 32 kg/m2. In general, the distribution of demographic variables and other baseline medical conditions was similar in the three groups. Most substudy subjects were considered by the Applicant to be primary prevention subjects (73% for celecoxib, 81% for ibuprofen, and 84% for naproxen) and the remainder to be secondary prevention subjects. The use of aspirin at baseline averaged 48%, also distributed evenly across all treatment groups.

Almost all (99.5%) substudy subjects took at least one concomitant medication. Most commonly, this involved aspirin, hydrochlorothiazide, lisinopril, metformin, or simvastatin. Overall, 12% of
substudy subjects in the mITT population were taking anti-hypertensive medication, with 13% in the celecoxib group, 11% in the ibuprofen group, and 13% in the naproxen group.

4.2.2.3 Applicant’s analysis

4.2.2.3.1 Summary of results
Among the total of 444 analyzable subjects, at Month 4, celecoxib-treated subjects had the smallest change in 24-hour ambulatory SBP compared with ibuprofen and naproxen: celecoxib resulted in a slight reduction of -0.3 mmHg while ibuprofen and naproxen increased mean 24-hour SBP by 3.7 and 1.6 mmHg, respectively. These changes resulted in a statistically significant difference of -3.9 mmHg (p=0.0009) between celecoxib and ibuprofen; a non-significant difference of -1.8 mmHg (p=0.119) between celecoxib and naproxen, and a non-significant difference of -2.1 mmHg (p=0.0787) between naproxen and ibuprofen. The change in 24-hour SBP at Month 2 was similar to Month 4. The change in 24-hour DBP at Months 2 and 4 was not statistically significant for any of the treatment comparisons. None of the experimental treatments affected the normal circadian BP curves. The above described findings should be interpreted keeping in mind that the doses administered in the three treatment groups were not comparable (lower dose in the celecoxib group compared to higher doses in the ibuprofen and naproxen groups).

4.2.2.3.2 Primary Endpoint
At Month 4, there was a small reduction of -0.3 mmHg in mean 24-hour SBP in the celecoxib group, and an increase in the ibuprofen and naproxen groups of 3.7 and 1.6 mmHg, respectively (Table 28). The difference between ibuprofen and celecoxib of -3.9 mmHg was statistically significant (p=0.0009). The MMRM sensitivity analysis demonstrated comparable results. None of the experimental drug treatments affected the “normal” circadian BP curves such that all groups demonstrated a lowering of BP in the evening and a rise in the early morning hours.
4.2.2.3.3 Secondary Endpoints

4.2.2.3.3.1 Change in mean 24-hour ambulatory SBP at Month 2 from Baseline

As shown in Table 29, for Month 2, an increase in mean 24-hour ambulatory SBP compared to baseline was observed in all treatment groups: 0.7 mmHg for celecoxib, 4.0 mmHg for ibuprofen, and 1.1 mmHg for naproxen. The difference between ibuprofen and celecoxib of -3.3 mmHg was statistically significant (p=0.0049), as was the difference between naproxen and ibuprofen (-2.9 mmHg; p=0.0144).

Table 29: Mean 24-hour ambulatory systolic BP: Baseline, Month 2, and change from baseline

<table>
<thead>
<tr>
<th>Mean 24-hour Ambulatory SBP (mmHg)</th>
<th>Celecoxib 100-200 mg BID (N=134)**</th>
<th>Ibuprofen 600-800 mg TID (N=142)**</th>
<th>Naproxen 375-500 mg BID (N=137)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Mean (SD)</td>
<td>124.2 (12.4)</td>
<td>125.2 (11.8)</td>
<td>123.6 (11.0)</td>
</tr>
<tr>
<td>Month 2 Mean (SD)</td>
<td>124.9 (13.5)</td>
<td>129.0 (13.8)</td>
<td>124.9 (13.0)</td>
</tr>
<tr>
<td>Change from Baseline LS Mean (SE)</td>
<td>0.7 (1.0)</td>
<td>4.0 (1.0)</td>
<td>1.1 (1.0)</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Celecoxib vs. Naproxen</td>
<td>Celecoxib vs. Ibuprofen</td>
<td>Naproxen vs. Ibuprofen</td>
</tr>
<tr>
<td>Change from Baseline Difference LS Mean (SE)</td>
<td>-0.4 (1.2)</td>
<td>-3.3 (1.2)</td>
<td>-2.9 (1.2)</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.7136</td>
<td>0.0049</td>
<td>0.0144</td>
</tr>
</tbody>
</table>

(Source: Applicant’s Table 5 from ABPM substudy report, page 38)
4.2.2.3.3.2 Change in mean 24-hour ambulatory DBP at Month 4 and Month 2 from Baseline

As shown in Table 30, for Month 4, there was a slight increase in mean 24-hour ambulatory DBP for the three treatment groups: 0.2 mmHg for celecoxib, 0.8 mmHg for ibuprofen, and 0.7 mmHg for naproxen. The differences between treatment groups were not statistically significant. The findings were similar for the change in mean 24-hour ambulatory DBP at Month 2 from baseline.

Table 30: Mean 24-hour ambulatory diastolic BP: baseline, Month 4, and change from baseline

<table>
<thead>
<tr>
<th>Mean 24-hour Ambulatory DBP (mmHg)</th>
<th>Celecoxib 100-200 mg BID (N=146)</th>
<th>Ibuprofen 600-800 mg TID (N=151)</th>
<th>Naproxen 375-500 mg BID (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Mean (SD)</td>
<td>70.9 (8.0)</td>
<td>70.5 (8.5)</td>
<td>70.1 (7.4)</td>
</tr>
<tr>
<td>Month 4 Mean (SD)</td>
<td>70.9 (8.8)</td>
<td>71.3 (9.0)</td>
<td>70.9 (7.9)</td>
</tr>
<tr>
<td>Change from Baseline LS Mean (SE)</td>
<td>0.2 (0.6)</td>
<td>0.8 (0.6)</td>
<td>0.7 (0.6)</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Celecoxib vs. Naproxen</td>
<td>Celecoxib vs. Ibuprofen</td>
<td>Naproxen vs. Ibuprofen</td>
</tr>
<tr>
<td>Change from Baseline Difference LS Mean (SE)</td>
<td>-0.5 (0.7)</td>
<td>-0.7 (0.7)</td>
<td>-0.1 (0.7)</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.4552</td>
<td>0.3565</td>
<td>0.8658</td>
</tr>
</tbody>
</table>

(Source: Applicant’s Table 6 from ABPM substudy report, page 48)

4.2.2.3.3.3 Change in mean 24-hour ambulatory MAP at Month 2 and Month 4 from Baseline

At Month 2, there was an increase in mean 24-hour MAP compared to baseline for all treatment groups: in the celecoxib group 0.3 mmHg, in the ibuprofen group 2.1 mmHg, and in the naproxen group 0.5 mmHg. The difference between ibuprofen and celecoxib (-1.8 mmHg, p=0.0319) was statistically significant.

At Month 4, there was no change in mean 24-hour ambulatory MAP in the celecoxib group, a small increase in the ibuprofen group (1.8 mmHg), and a small increase in the naproxen group (1.1 mmHg) compared to baseline. The difference between ibuprofen and celecoxib (-1.8 mmHg, p=0.0385) was statistically significant.
4.2.2.3.4 Change in mean 24-hour ambulatory Pulse Pressure (PP) at Month 4 from Baseline

At Month 4, there was a slight decrease in mean 24-hour ambulatory PP in the celecoxib group (-0.3 mmHg), an increase in the ibuprofen group (2.7 mmHg), and a small increase in the naproxen group (1.0 mmHg) compared to baseline. The difference between ibuprofen and celecoxib (-3.0 mmHg, p<0.0001) and between naproxen and ibuprofen (-1.7 mmHg; p=0.0109) was statistically significant. Similar results were observed at Month 2.

4.2.2.4 Division of Cardiovascular and Renal Products (DCRP)’s Assessment of the ABPM substudy

DAAAP requested input from DCRP on the clinical significance of the findings from the ABPM substudy.

The DCRP reviewer, Dr. Tzu-Yun McDowell, was able to replicate the results of the primary analysis. The p-values of her analysis were larger (Table 31) but the difference between celecoxib versus ibuprofen was still below the pre-defined significance level of 0.0167.

Table 31: Differences in BP among treatment groups (ABPM substudy)

<table>
<thead>
<tr>
<th>Change from baseline at Month 4</th>
<th>Least Square mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Celecoxib vs. Ibuprofen</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td></td>
</tr>
<tr>
<td>SBP&lt;sub&gt;24h&lt;/sub&gt;</td>
<td>-3.9 (-6.7, -1.2)</td>
</tr>
<tr>
<td></td>
<td>p=0.003</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td></td>
</tr>
<tr>
<td>SBP&lt;sub&gt;awake&lt;/sub&gt;</td>
<td>-4.2 (-7.1, -1.3)</td>
</tr>
<tr>
<td>SBP&lt;sub&gt;sleep&lt;/sub&gt;</td>
<td>-3.4 (-6.6, -0.2)</td>
</tr>
<tr>
<td>DBP&lt;sub&gt;24h&lt;/sub&gt;</td>
<td>-0.7 (-2.4, 1.0)</td>
</tr>
<tr>
<td>DBP&lt;sub&gt;awake&lt;/sub&gt;</td>
<td>-0.5 (-3.3, 2.3)</td>
</tr>
<tr>
<td>DBP&lt;sub&gt;sleep&lt;/sub&gt;</td>
<td>-0.9 (-2.9, 1.1)</td>
</tr>
<tr>
<td>MAP&lt;sub&gt;24h&lt;/sub&gt;</td>
<td>-1.7 (-3.7, 0.2)</td>
</tr>
<tr>
<td>PP&lt;sub&gt;24h&lt;/sub&gt;</td>
<td>-3.0 (-4.6, -1.4)</td>
</tr>
</tbody>
</table>

(Source: Table created by Dr. Tzu-Yun McDowell)

According to Dr. McDowell’s review, “…at any point of time, celecoxib ambulatory SBP profile at Month 4 nearly matched that observed at baseline. On the contrary, there was a noticeable upward shift of the ambulatory SBP profile at Month 4 for ibuprofen compared to that observed at baseline. The greater increase in SBP by ibuprofen was observed during daytime between 9 am to 2 pm with an average increase in SBP of ~4-6 mmHg.
Naproxen was associated with an intermediate effect on ambulatory SBP when compared to celecoxib and ibuprofen.” (Figures 6, 7, and 8)

**Figure 6: Baseline and Month 4 24-hour ambulatory systolic BP profile for celecoxib**

![Graph showing the baseline and Month 4 24-hour ambulatory systolic BP profile for celecoxib](source)

(Source: Figure created by Dr. Tzu-Yun McDowell)

**Figure 7: Baseline and Month 4 24-hour ambulatory systolic BP profile for ibuprofen**

![Graph showing the baseline and Month 4 24-hour ambulatory systolic BP profile for ibuprofen](source)

(Source: Figure created by Dr. Tzu-Yun McDowell)
Figure 8: Baseline and Month 4 24-hour ambulatory systolic BP profile for naproxen

Dr. McDowell stated that the relationship between BP, in particular SBP, and risk of CV events increases progressively with increasing BP. She cited published literature suggesting that decreasing the SBP or DBP “by even modest amounts (i.e., 2-3 mmHg) has the potential to reduce CV morbidity and mortality substantially.” She explained that “in light of this compelling evidence, CV outcome claims were added for all antihypertensive drugs per the 2011 Guidance for Industry.”

To address the question of the clinical importance of the small changes in SBP noted for the comparator drugs in the ABPM substudy compared to the negligible changes in the celecoxib group, she explained the following:

“Despite the well-established relationship between BP and CV risk, it is difficult to define precisely the CV risk for a non-CV drug that causes a small increase in BP because an individual’s CV risk depends on multiple factors (i.e. baseline risk, baseline BP and duration of treatment). The modest increase in SBP (~4 mmHg) by ibuprofen is expected to increase the relative risk for major CV events (i.e. MI, stroke and death), if sustained with chronic therapy. However, the absolute increase in CV events will be much greater in patients with higher baseline CV risk for reasons other than BP (i.e. prior history of CV events and or other CV risk factors such as diabetes or smoking). Another important factor to consider is duration of therapy. In general, there is little concern about a drug intended for short-term use that has modest effects on BP. However, greater concern should be made for drugs that are used chronically, particularly if indicated population has high background CV risk.”
In summary, after 4 months of treatment, the SBP was minimally changed with celecoxib but rose by a mean of ~4 mmHg with ibuprofen and <2 mmHg with naproxen. The difference between celecoxib and ibuprofen (−3.9 mmHg) reached pre-defined statistical significance level of 0.0167. In response to the DAAAP question for the clinical significance of the −3.9 mmHg difference in 24-hour SBP observed between celecoxib and ibuprofen, Dr. McDowell stated that “a small decrement in BP in the general population, as little as 2-3 mmHg in SBP, would result in substantial reductions in CV risk. Hence, DCRP believes that ~4 mm Hg increase in SBP, if sustained with chronic therapy, can be reasonably expected to progressively increase the CV events in successive decades of life. This risk increases in patients with established CV disease and multiple CV risk factors.”
5 Clinical Efficacy Summary

5.1 Patient’s assessment of arthritis pain

Measurement of arthritis pain was a secondary endpoint in PRECISION. The patient’s assessment of arthritis pain was evaluated at baseline and subsequent study visits, using a 100-mm visual analogue scale (VAS). Although study visits occurred at infrequent intervals (including baseline and months 1, 2, 4, 8, 12, 18, 24, 30, 36, and 42), the Applicant believed this schedule allowed for adequate assessment of how well the treatments were working. Subjects were asked to rate their pain according to the following question: “How much pain are you having because of your arthritis?”

The protocol did not require documentation of response or failure to treatment with NSAIDs prior to enrollment. Over-the-counter and prescription NSAIDs and selective COX-2 inhibitors, other than the provided study drugs, were prohibited for use during the study. However, patients were not prohibited from continuing stable pain therapies, outside the NSAID class during the study.

The following rescue medications were allowed for breakthrough arthritis pain:

- Acetaminophen or non-NSAID combination product
- Opioid; tramadol
- Duloxetine
- Intra-articular steroid or hyaluronic acid

The protocol did not describe how the pain assessments accounted for the use of rescue medication.

Version 5 of the statistical analysis plan (SAP) from July 28, 2016 described that the change in patient’s assessment of pain was analyzed using Mixed Model Repeated Measurements (MMRM) with baseline score as the covariate. For early terminations, the last unplanned observation was used to impute missing data for the next visit within 30 days. No adjustments were made for multiple comparisons.

The Applicant reported that in each treatment group, subjects indicated an improvement from baseline in arthritic pain by 8 mm mean reduction in VAS scores at Month 1, and then by 10 mm mean reductions at Month 2. The improvement of 10 mm stayed stable through Month 42. The differences between treatment groups were small, ranging from 0 mm to 1.8 mm. The Applicant reported statistically significant differences at Month 1 for the celecoxib group compared with the naproxen group (mean change: -8.2 vs. -9.9: P<0.0001 [ITT]), for the celecoxib group compared with the ibuprofen group (mean change: -8.2 vs.-9.0: P=0.0373 [ITT]), and for the ibuprofen group compared with the naproxen group (mean change: -9.0 vs. -9.9: P=0.0129 [ITT]). No statistically significant differences in VAS were observed from Month 2 to Month 36 among the 3 treatment groups. Table 1 includes data from baseline and Month 1.
Table 1: Change from baseline to Month 1 visit in patient’s assessment of pain (VAS) - ITT

(Source: Applicant’s table 14.2.10.1.1.1 from study report body)

Similar results are reported for the tertiary endpoints of Patient’s Global Assessment of Arthritis and Health assessment questionnaire disability index (HAQ-DI).

The global assessment of arthritis question asked, “How are you doing today,” and was graded on a scale from 1 to 5, with 1 indicating that the subject assessed their disease state as very good (asymptomatic with no limitation of daily activity) and 5 meaning that the subject assessed their disease status as very poor (very severe symptoms and inability to carry out all normal activities). In all treatment groups, subjects indicated an improvement in global assessment for arthritis with very small score reductions (mean of -0.2 to -0.3) compared with baseline.

In summary, there were multiple concerns, as listed below, with the assessments of pain and efficacy analysis used in PRECISION:

- Analysis of the pain endpoints was not the primary objective of the study
• Establishing a baseline pain score:
  o Wash-out of pain medications that the subject was taking prior to study enrollment was not required.
  o It is not clear if the baseline pain score was collected while patients were receiving pain medications for their arthritis.
  o If the baseline pain score was not assessed properly, then any change from baseline would be uninterpretable
• Pain was not adequately measured during the study:
  o Patient diaries were not used
  o Investigators asked patients to rate their arthritis pain during clinic visits that occurred infrequently and therefore did not allow for adequate assessment of how well the treatments were working
• Use of MMRM analysis which assumes that data are missing at random
• No adjustment for multiplicity

Regardless of these shortcomings in study design with respect to efficacy, the change in baseline pain at month 4 (week 16) was evaluated using continuous responder curves. In these curves subjects that discontinued or had bad outcomes are considered as having no improvement in pain scores. Percent of subjects is shown on the y-axis and the percent improvement is shown on the x-axis. This figure does not show the data from subjects that discontinued or those whose baseline pain did not improve. Results are shown in Figure 1.

Figure 1: Continuous responder curves

Regardless of treatment, there is clearly no separation in these curves.
6 Statistical Summary

6.1 Study Objectives

The primary objective of the PRECISION trial was to assess the effects of celecoxib 100-200 mg twice daily (bid) compared to naproxen 375-500 mg bid on the first occurrence of the Antiplatelet Trialists Collaboration (APTC) composite cardiovascular (CV) endpoint (non-fatal myocardial infarction [MI], non-fatal stroke, CV Death) in subjects with osteoarthritis (OA) or rheumatoid arthritis (RA) with established cardiovascular disease (CVD) or risk factors for CVD. CV effects of celecoxib 100-200 mg bid compared to ibuprofen 600-800 mg three times daily (TID), and ibuprofen 600-800 mg TID compared to naproxen 375-500 mg bid were also assessed.

The statistical design of PRECISION was based on demonstrating non-excessive risk (i.e. non-inferiority) of APTC events in subjects treated with celecoxib relative to subjects treated with naproxen. The hazard ratio (HR) and 95% confidence interval (CI) for each pair-wise treatment comparison (celecoxib vs. naproxen, celecoxib vs. ibuprofen, and ibuprofen vs. naproxen) was estimated using a Cox proportional hazards (PH) model. Non-excessive risk of APTC events for each specific treatment comparison would be demonstrated if the following 3 criteria were met:

1) The upper bound of the two-sided 95% CI of the HR did not exceed 1.33 in the primary intent-to-treat (ITT) analysis;
2) The upper bound of the two-sided 95% CI of the HR did not exceed 1.40 in a modified intent-to-treat (MITT) analysis;
and
3) The point estimate of the HR for both the ITT and MITT analyses did not exceed 1.12.

In the primary analysis, celecoxib would be considered to have demonstrated non-excessive CV risk compared to other NSAIDs (ibuprofen or naproxen) only if non-excessive risk of APTC for both comparisons of celecoxib versus ibuprofen and celecoxib versus naproxen were demonstrated.

PRECISION was an event-driven cardiovascular outcomes trial (CVOT). Each pair-wise treatment comparison required 387 APTC events in the ITT analysis to have 80% power to rule out a 33% increase of CV risk (580 total events across the three treatment arms). Each pair-wise treatment comparison required 278 APTC events in the MITT analysis to have 80% power to rule out a 40% increase of CV risk (420 total events across the three treatment arms).26

Secondary objectives of the PRECISION trial included the assessment of other measures of CV safety as well as gastrointestinal (GI) safety, renal safety, and arthritis efficacy.

26 PRECISION was originally planned with 90% power to evaluate noninferiority; however, a lower than expected APTC event accrual rate led to a protocol amendment to lower the power to 80%; the non-inferiority boundary was changed from 1.33 to 1.40 for mITT (Per Protocol) analysis, and the data were truncated at 30 months for ITT analysis and 42 months (+30 days) for Per Protocol analysis.
6.2 Statistical Methods
6.2.1 Endpoints, Event Ascertainment and Adjudication

The pre-specified primary endpoint in PRECISION is the first occurrence of a composite endpoint consisting of CV death, non-fatal MI, and non-fatal stroke, referred to as the APTC endpoint.

Protocol-defined secondary endpoints of PRECISION include the following:

- The first occurrence of major adverse cardiovascular event (MACE), defined as the composite of CV death, non-fatal MI, non-fatal stroke, revascularization, hospitalization for unstable angina (UA), or hospitalization for transient ischemic attack (TIA).
- The occurrence of clinically significant gastrointestinal events (CSGIEs).
- Patient’s Assessment of Arthritis Pain (VAS).

Among the secondary endpoints described above, only the analysis of MACE endpoint is presented in this review due to its relevance to the CV safety assessment. In addition, all-cause mortality was considered an important element for the assessment of CV safety and general safety of celecoxib in this review. The analyses of secondary and tertiary endpoints were not part of a pre-specified hierarchical statistical testing plan therefore they were considered as exploratory.

Per study protocol, following randomization, clinic visits were scheduled at Months 1, 2, 4, 8, and 12, and every 6 months thereafter through 42 months to collect and assess pre-specified measures of efficacy and safety. All subjects who discontinued study drug prematurely would continue to be followed per protocol-defined visit timepoints and assessments through Month 42 or the event-driven end of the study, whichever occurred first. All subjects were to be contacted by telephone 30 days after their study drug discontinuation for follow-up assessment of serious adverse events and study endpoints that may have occurred since their last day on active treatment.

An independent and blinded Clinical Events Committee (CEC) reviewed and adjudicated all CV, GI, renal and anemia events in accordance with pre-specified definitions.

6.2.2 Analysis Sets and Censoring Window

The pre-specified evaluation of CV safety in PRECISION utilized two analysis sets:

- The intent-to-treat (ITT) analysis set consisted of all randomized subjects. Subjects in the ITT population were analyzed as randomized.
- The modified intent-to-treat (MITT) analysis set consisted of all randomized subjects who received at least one dose of study drug, and had at least one post-baseline visit. Subjects in the MITT population were analyzed as randomized.

The primary analyses of APTC events were based upon time-to-event methodologies utilizing the following two censoring schemes:

1) The ITT analysis includes all positively adjudicated first APTC events that occurred in the ITT population between randomization and 30 months since randomization or last known follow-up date, whichever is earlier. This censoring scheme will be referred to as “on study through 30 months” for the rest of the review.
2) The MITT analysis includes all positively adjudicated first APTC events that occurred in the MITT population between randomization and 30 days after the last dose of the study medication or last known follow-up date, whichever is earlier. This censoring scheme will be referred to as “on treatment + 30 days” for the rest of the review.

6.2.3 Pre-Specified Primary Analysis of the APTC Endpoint
In the primary time-to-event analysis, the hazard ratio and its associated 95% CI for each pairwise treatment comparison was estimated using a Cox proportional hazards model for the ITT analysis (“on study through 30 months” censoring) and repeated for the MITT analysis (“on treatment + 30 days” censoring) as defined above. The Cox model included covariates for region, baseline diagnosis of arthritis (OA or RA), and baseline use of low-dose aspirin for cardio-protection (use or no use).

6.2.4 Sensitivity Analysis of the APTC Endpoint
A sensitivity analysis was conducted by the Applicant to evaluate whether primary analysis results would be impacted by potential informative censoring (subjects who discontinued study prematurely could be at higher risk to develop a primary APTC event than subjects who remained in the study). Potential informative censoring may have occurred when subjects withdrew from the study due to non-administrative reasons including loss to follow-up, no longer willing to participate in the study, and withdrawn consent.

The incidence rate of APTC events was calculated separately for subjects with and without any of the following pre-identified classes of adverse events (AEs) during the study through 30 months. These AEs were pre-identified based on their potential association with myocardial events or vascular events:

- Bleeding (>2 g Hgb drop, hospitalization for bleeding, hemorrhage);
- Chest pain (including angina and chest discomfort);
- Hypertension out of control (leading to hospitalization or emergency room visit);
- Diabetes out of control (leading to hospitalization or emergency room visit);
- Renal failure (e.g. increase in creatinine by >1 mg/dL);
- TIA;
- Syncope or near syncope.

Subjects who experienced these AEs were identified according to MedDRA terms. The observed incidence rate of APTC events among subjects with and without these AEs across all 3 treatment arms was used to impute the expected number of APTC events among subjects with early study withdrawal based on their observed adverse events during their on-study period and their expected missing observation time. The imputed events were then combined with the observed APTC events for the primary ITT analysis (on study through 30 months) in a logistic regression model with treatment as the only covariate to calculate the odds ratio (OR) and its associated 95% CI, to evaluate the impact of potential informative censoring on the primary analysis results of APTC.

The sensitivity analysis conducted by the applicant did not consider potential differential informative censoring across the three treatment arms. The reviewer conducted additional analyses to explore the impact of differential informative censoring on the primary analysis.
result of APTC, by assuming higher incidence rates of APTC among the early-withdrawal subjects on celecoxib than those on ibuprofen or naproxen. A tipping point analysis was conducted to assess how extreme the imbalance would need be to alter the study conclusion.

6.2.5 Subgroup Analyses of the APTC Endpoint
The time to first occurrence of APTC was evaluated for each treatment comparison within the subgroups of age, gender, race, region, baseline aspirin use, primary diagnosis of RA or OA, evidence of established CVD, baseline diabetes, and baseline smoking status for both the ITT and MITT analyses. These findings are presented in this document.

6.2.6 Analysis of Secondary Endpoints
The PRECISION trial was designed to evaluate the risk of APTC between each pair-wise treatment comparison. A hierarchical statistical testing plan was not pre-specified, therefore, the evaluation of secondary endpoints and all other endpoints, including MACE and all-cause mortality, is considered descriptive/supportive only.

For time-to-event analysis of MACE and all-cause mortality, a similar Cox proportional hazards model as that used for the analysis of the primary endpoint APTC was used to calculate the hazard ratio and its corresponding nominal 95% CI (uncorrected for multiplicity) for each treatment comparison based on both ITT analysis using the “on study through 30 months” censoring scheme and MITT analysis using the “on treatment + 30 days” censoring window.

6.3 Results
6.3.1 Subject Disposition
An overview of subject disposition by treatment group is summarized in Table 1. A total of 24081 subjects (ITT population) were randomized in the PRECISION trial, of which 23955 (99.5%) were treated and 23953 were treated with at least one post-baseline study visit (MITT population). In the ITT population, 16865 (70.0%) subjects completed the study and 7031 (29.2%) subjects discontinued study prematurely (including deaths). A total of 7511 (31.2%) subjects completed the study treatment regimen while 16308 (67.7%) subjects discontinued treatment early. Percentages of premature study discontinuation and treatment discontinuation appear similar across the 3 randomized groups. Please refer to the clinical review by Dr. Pokrovnichka for additional details of subject disposition.
Table 1: Subject Disposition

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib (N= 8072)</th>
<th>Ibuprofen (N= 8040)</th>
<th>Naproxen (N= 7969)</th>
<th>Total (N= 24081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (ITT)</td>
<td>8072 (100%)</td>
<td>8040 (100%)</td>
<td>7969 (100%)</td>
<td>24081 (100%)</td>
</tr>
<tr>
<td>Completed study</td>
<td>5664 (70.2%)</td>
<td>5580 (69.4%)</td>
<td>5621 (70.5%)</td>
<td>16865 (70.0%)</td>
</tr>
<tr>
<td>Discontinued study</td>
<td>2346 (29.1%)</td>
<td>2399 (29.8%)</td>
<td>2286 (28.7%)</td>
<td>7031 (29.2%)</td>
</tr>
<tr>
<td>Missing EOS status*</td>
<td>62 (0.8%)</td>
<td>61 (0.8%)</td>
<td>62 (0.8%)</td>
<td>185 (0.8%)</td>
</tr>
<tr>
<td>Treated</td>
<td>8030 (99.5%)</td>
<td>7992 (99.4%)</td>
<td>7933 (99.5%)</td>
<td>23955 (99.5%)</td>
</tr>
<tr>
<td>Completed treatment</td>
<td>2623 (32.5%)</td>
<td>2363 (29.4%)</td>
<td>2525 (31.7%)</td>
<td>7511 (31.2%)</td>
</tr>
<tr>
<td>Discontinued treatment</td>
<td>5363 (66.4%)</td>
<td>5584 (69.5%)</td>
<td>5361 (67.3%)</td>
<td>16308 (67.7%)</td>
</tr>
<tr>
<td>Missing EOT status**</td>
<td>44 (0.5%)</td>
<td>45 (0.6%)</td>
<td>47 (0.6%)</td>
<td>136 (0.6%)</td>
</tr>
<tr>
<td>Not treated</td>
<td>42 (0.5%)</td>
<td>48 (0.6%)</td>
<td>36 (0.5%)</td>
<td>126 (0.5%)</td>
</tr>
<tr>
<td>MITT: Treated with at least 1 post-baseline visit</td>
<td>8030 (99.5%)</td>
<td>7990 (99.4%)</td>
<td>7933 (99.5%)</td>
<td>23953 (99.5%)</td>
</tr>
</tbody>
</table>

*: End of study (EOS) status was missing on the end of study page of case report form (CRF).
**: End of treatment (EOT) status was missing on the end of treatment page of CRF.
Source: created by reviewer.

Table 2 below summarizes the duration of subject follow up through the end of the study, duration of subject follow up through 30 months, and treatment exposure, respectively. The distributions of subject follow up and treatment exposure are similar for the three treatment arms.

Table 2: Subject Follow-up and Treatment Exposure

<table>
<thead>
<tr>
<th>Subject Follow-up (ITT)</th>
<th>Celecoxib (N= 8072)</th>
<th>Ibuprofen (N= 8040)</th>
<th>Naproxen (N= 7969)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months of follow up through study end</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>34.4 (13.4)</td>
<td>34.0 (13.7)</td>
<td>34.4 (13.4)</td>
</tr>
<tr>
<td>Median</td>
<td>42.2</td>
<td>42.1</td>
<td>42.2</td>
</tr>
<tr>
<td>Max</td>
<td>79.9</td>
<td>89.6</td>
<td>86.1</td>
</tr>
<tr>
<td>Months of follow up through 30 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>25.8 (8.1)</td>
<td>25.6 (8.3)</td>
<td>25.8 (8.0)</td>
</tr>
<tr>
<td>Median</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Exposure (Treated)</th>
<th>Celecoxib (N= 8030)</th>
<th>Ibuprofen (N= 7992)</th>
<th>Naproxen (N= 7933)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months of treatment exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>20.9 (16.1)</td>
<td>19.7 (16.1)</td>
<td>20.6 (16.0)</td>
</tr>
<tr>
<td>Median</td>
<td>18.5</td>
<td>16.2</td>
<td>18.2</td>
</tr>
<tr>
<td>Max</td>
<td>51.2</td>
<td>58.5</td>
<td>82.0</td>
</tr>
</tbody>
</table>

Source: created by reviewer.
As shown in Figure 1, study discontinuation was gradual and the distribution of the time to early study discontinuation appears similar in all treatment arms. Overall, approximately 20.6% of the ITT subjects withdrew from the study early by 30 months since randomization, and early study discontinuation rates were balanced over time across the 3 comparison arms.

Figure 1: Kaplan-Meier Plot of Time to Early Study Discontinuation (ITT)

![Kaplan-Meier Plot](image)

Source: created by reviewer.

Table 3 below depicts early study discontinuation rates by the year of enrollment/randomization for all randomized subjects. The highest study discontinuation rates were observed among subjects who enrolled in the trial between 2006 and 2008. Subject retention appears to have improved among subjects who were randomized after the first 2 years of the trial (2008).

<table>
<thead>
<tr>
<th>Enrollment Period</th>
<th>N</th>
<th>Early Withdrawal (%)</th>
<th>Early Withdrawal by Month 18 (%)</th>
<th>Early Withdrawal by Month 24 (%)</th>
<th>Early Withdrawal by Month 30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/21/2006 – 10/20/2008</td>
<td>8343</td>
<td>34.4</td>
<td>17.8</td>
<td>21.3</td>
<td>25.0</td>
</tr>
<tr>
<td>10/21/2008 – 10/20/2010</td>
<td>6271</td>
<td>30.6</td>
<td>12.0</td>
<td>15.9</td>
<td>19.2</td>
</tr>
<tr>
<td>10/21/2010 – 10/20/2012</td>
<td>4443</td>
<td>28.8</td>
<td>10.9</td>
<td>14.1</td>
<td>18.1</td>
</tr>
<tr>
<td>10/21/2012 – 06/30/2014</td>
<td>5024</td>
<td>19.2</td>
<td>11.0</td>
<td>14.9</td>
<td>17.3</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>24081</td>
<td>29.2</td>
<td>13.6</td>
<td>17.2</td>
<td>20.6</td>
</tr>
</tbody>
</table>

Source: created by reviewer.
Figure 2 shows the distribution of the time to premature treatment discontinuation by treatment arm in the treated subjects. The ibuprofen group showed a slightly higher treatment discontinuation rate than the celecoxib and naproxen arms throughout the study.

Figure 2: Kaplan-Meier Plot of Time to Early Treatment Discontinuation (Treated)

Source: created by reviewer.

6.3.2 Primary Analysis of APTC

The primary analysis results of the primary APTC endpoint are presented in Table 4. Note that only the results of treatment comparisons involving celecoxib (C vs. I = celecoxib versus ibuprofen; C vs. N = celecoxib versus naproxen) are presented in the following sections. The pre-specified Cox proportional hazards model was used to evaluate the risk of APTC associated with celecoxib compared with ibuprofen or naproxen. Based on this model, the estimated hazard ratio of APTC for celecoxib vs. naproxen in the ITT analysis is 0.93 with 95% confidence interval (0.76, 1.13), while the estimated HR in the MITT analysis is 0.91 with a 95% CI of (0.72, 1.15). This analysis demonstrated that celecoxib is not associated with an elevated risk of APTC compared to naproxen per the pre-specified criteria. Similarly, the conclusion of non-excessive risk of APTC events can be reached regarding the treatment comparison of celecoxib vs. ibuprofen.

Table 4: Primary Analysis Results of APTC

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (on study through 30 months)</td>
<td>N= 8072</td>
<td>N= 8040</td>
<td>N= 7969</td>
</tr>
<tr>
<td>Number (%) of APTC</td>
<td>188 (2.3)</td>
<td>218 (2.7)</td>
<td>201 (2.5)</td>
</tr>
<tr>
<td>Incidence Rate per 100 Person-years</td>
<td>1.1</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Pairwise Comparison</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C vs. I</td>
<td>0.86 (0.70, 1.04)</td>
<td></td>
<td>0.93 (0.76, 1.13)</td>
</tr>
<tr>
<td>MITT (on treatment + 30 days)</td>
<td>N= 8030</td>
<td>N= 7990</td>
<td>N= 7933</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Number (%) of APTC</td>
<td>134 (1.7)</td>
<td>155 (1.9)</td>
<td>144 (1.8)</td>
</tr>
<tr>
<td>Incidence Rate per 100 Person-years</td>
<td>0.9</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Pairwise Comparison HR (95% CI)</td>
<td>C vs. I 0.81 (0.64, 1.02)</td>
<td>C vs. N 0.91 (0.72, 1.15)</td>
<td></td>
</tr>
</tbody>
</table>

Source: created by reviewer.

Figure 3 and Figure 4 show the Kaplan-Meier (K-M) cumulative probability of developing APTC for the three treatment arms in the ITT analysis and MITT analysis respectively. The K-M curves resemble straight lines in these observation intervals (30 months for the ITT and 42 months for the MITT analyses) and suggest that the APTC event rate was approximately constant over time within each treatment arm in PRECISION.

In both the ITT and MITT analyses, the K-M curves for celecoxib and naproxen are generally close to each other and the ibuprofen arm shows a numerically slightly higher proportion of subjects who experienced a primary APTC event.

**Figure 3: Kaplan-Meier Plot of Time to First APTC (ITT, on study through 30 months)**

![Kaplan-Meier Plot](image)
6.3.3 Analysis of the Components of the Primary Endpoint

An exploratory analysis of the components of the primary composite endpoint (i.e., CV death, non-fatal MI, and non-fatal stroke) is presented in Table 5 below for the ITT analysis based on the “on study through 30 months” censoring window. The hazard ratio for each component was calculated using a similar Cox regression model as that used in the primary analysis. The 95% confidence interval for each of the 3 components includes the null value of 1 for the treatment comparisons celecoxib vs. ibuprofen and celecoxib vs. naproxen, with a HR estimate numerically favoring the celecoxib arm except for the HR of non-fatal MI (1.14) comparing celecoxib vs. naproxen.
Table 5: Analysis Results for Components of APTC (ITT, on study through 30 months)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib (N= 8072)</th>
<th>Ibuprofen (N= 8040)</th>
<th>Naproxen (N= 7969)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTC Pairwise Comparison</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>C vs. I</td>
<td>0.86 (0.70, 1.04)</td>
<td>0.93 (0.76, 1.13)</td>
<td></td>
</tr>
<tr>
<td>C vs. N</td>
<td>0.86 (0.70, 1.04)</td>
<td>0.93 (0.76, 1.13)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APTC Component</th>
<th>CV Death</th>
<th>HR (95% CI)</th>
<th>Non-fatal MI</th>
<th>HR (95% CI)</th>
<th>Non-fatal Stroke</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.84 (0.61, 1.16)</td>
<td>0.78 (0.57, 1.07)</td>
<td>1.14 (0.82, 1.59)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: created by reviewer.

6.3.4 Sensitivity Analysis to Evaluate Informative Censoring

The results of the sensitivity analysis assessing informative censoring are presented in Table 6. The incidence rate of APTC events was calculated separately for subjects with and without any of the selected AEs listed in Section 2.4, based on observed data in the trial. The incident rate of APTC observed in subjects with the selected AEs was 2.83 per 100 person-years, while the incidence rate was 0.91 per 100 person-years in subjects without these AEs. These incidence rates were used to impute the expected number of APTC events among subjects who withdrew study early based on their expected missing observation time: 20, 22 and 20 APTC events were imputed for the celecoxib, ibuprofen and naproxen arms, respectively. A logistic regression model with treatment as the explanatory variable was used to estimate the odds ratio and its corresponding 95% CI for APTC based on the sum of the observed and the imputed data. The upper bounds of the 95% CI for the odds ratios comparing celecoxib vs. naproxen (1.12) and celecoxib vs. ibuprofen (1.04) are similar to the upper bounds of the 95% confidence interval for hazard ratio estimated in the primary ITT analysis of APTC and therefore do not alter the conclusion of non-excessive risk of APTC associated with celecoxib relative to the other two NSAIDs.

Table 6: Sensitivity Analysis of APTC (ITT, on study through 30 months)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib (N= 8072)</th>
<th>Ibuprofen (N= 8040)</th>
<th>Naproxen (N= 7969)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTC observed in the trial</td>
<td>188</td>
<td>218</td>
<td>201</td>
</tr>
<tr>
<td>Subjects withdrew early without APTC</td>
<td>1337</td>
<td>1368</td>
<td>1316</td>
</tr>
<tr>
<td>with selected AEs</td>
<td>78</td>
<td>122</td>
<td>82</td>
</tr>
<tr>
<td>without selected AEs</td>
<td>1259</td>
<td>1246</td>
<td>1234</td>
</tr>
<tr>
<td>Imputed APTC for early withdrawal</td>
<td>20</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>APTC (observed + imputed)</td>
<td>208</td>
<td>240</td>
<td>221</td>
</tr>
<tr>
<td>OR (95% CI) *</td>
<td>0.86 (0.71, 1.04)</td>
<td>0.93 (0.77, 1.12)</td>
<td></td>
</tr>
</tbody>
</table>

*: Odds ratio (OR) was estimated based on a logistic regression model with treatment group as the explanatory variable.
Source: created by reviewer.
Table 7 shows the results of the tipping point analysis. In order for the upper bound of the 95% CI for the odds ratio of APTC events associated with celecoxib to exceed the pre-set margin of 1.33, the imputed number of events in the celecoxib arm would have to be three times as large as in the naproxen arm and four times as large as in the ibuprofen arm. A total of 59 (20+39) APTC events would need to be imputed in celecoxib, compared to only 20 imputed on naproxen, for the odds ratio of APTC events associated with celecoxib relative to naproxen to be 1.11 (0.92, 1.33). Similarly, a total of 80 (20+60) APTC events would need to be imputed in celecoxib, compared to 22 on ibuprofen, for the odds ratio of APTC events associated with celecoxib relative to ibuprofen to be 1.12 (0.94, 1.33). This analysis implies that unobserved events that could have occurred in subjects after they withdrew from the trial early were unlikely to change the conclusions of the trial, unless the rate of APTC among these subjects was much higher (at least 3 times higher) in the celecoxib arm. This scenario appears unlikely because the rate and reason of study withdrawal were similar in all three treatment arms in PRECISION.

**Table 7. Tipping Point Analysis of APTC Events (ITT, on study through 30 months)**

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib N= 8072</th>
<th>Ibuprofen N= 8040</th>
<th>Naproxen N= 7969</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTC observed in the trial</td>
<td>188</td>
<td>218</td>
<td>201</td>
</tr>
<tr>
<td>Imputed APTC based on AEs and study withdrawal</td>
<td>20</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>APTC (observed + imputed) based on AEs</td>
<td>208</td>
<td>240</td>
<td>221</td>
</tr>
<tr>
<td>APTC needed for an upper bound ≥ 1.33 (C vs. N) OR (95% CI) *, C vs. N</td>
<td>247</td>
<td>221</td>
<td></td>
</tr>
<tr>
<td>Additional APTC needed on celecoxib to tip results</td>
<td>+ 39</td>
<td>1.11 (0.92, 1.33)</td>
<td></td>
</tr>
<tr>
<td>APTC needed for an upper bound ≥ 1.33 (C vs. I) OR (95% CI) *, C vs. I</td>
<td>268</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Additional APTC needed on celecoxib to tip results</td>
<td>+ 60</td>
<td>1.12 (0.94, 1.33)</td>
<td></td>
</tr>
</tbody>
</table>

*: Odds ratio (OR) was estimated based on a logistic regression model with treatment group as the explanatory variable.
Source: created by reviewer.

**6.3.5 Analysis of Secondary Endpoints**

Table 8 summarizes the number of first occurrence of MACE by treatment using the ITT population and the “on study through 30 months” censoring window. Hazard ratios were estimated through the same Cox proportional hazards model used in the primary endpoint analysis. The time-to-event analysis results of MACE are consistent with the results of the primary APTC event, while including more events in the analysis.
Table 8: Analysis Results of MACE (ITT, on study through 30 months)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib N= 8072</th>
<th>Ibuprofen N= 8040</th>
<th>Naproxen N= 7969</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE (%)</td>
<td>337 (4.2)</td>
<td>384 (4.8)</td>
<td>346 (4.3)</td>
</tr>
<tr>
<td>Pairwise Comparison</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.87 (0.75, 1.01)</td>
<td></td>
<td>0.97 (0.83, 1.12)</td>
</tr>
<tr>
<td>MACE Component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>68</td>
<td>80</td>
<td>86</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>76</td>
<td>92</td>
<td>66</td>
</tr>
<tr>
<td>Non-fatal Stroke</td>
<td>51</td>
<td>53</td>
<td>57</td>
</tr>
<tr>
<td>Revascularization</td>
<td>174</td>
<td>198</td>
<td>161</td>
</tr>
<tr>
<td>Hospitalization for UA</td>
<td>55</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Hospitalization for TIA</td>
<td>18</td>
<td>27</td>
<td>18</td>
</tr>
</tbody>
</table>

Source: created by reviewer.

The time-to-event analysis results of all-cause mortality are presented in Table 9 for on study censoring through 30 months and through the study end (1301 days), respectively. The analysis results are consistent no matter which censoring window was used: the highest number of deaths were observed in the naproxen arm, followed by the ibuprofen arm, and then the celecoxib arm. Note that this endpoint was not part of a pre-specified statistical testing hierarchy and therefore confidence intervals should be considered exploratory.

Table 9: Analysis Results of All-cause Mortality

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib N= 8072</th>
<th>Ibuprofen N= 8040</th>
<th>Naproxen N= 7969</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE Component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>132 (1.6)</td>
<td>142 (1.8)</td>
<td>163 (2.1)</td>
</tr>
<tr>
<td>All-cause Deaths, on study through 30 months (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pairwise Comparison</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.92 (0.73, 1.17)</td>
<td></td>
<td>0.80 (0.63, 1.00)</td>
</tr>
<tr>
<td>All-cause Deaths, on study through study end (%)</td>
<td>185 (2.3)</td>
<td>193 (2.4)</td>
<td>228 (2.9)</td>
</tr>
<tr>
<td>Pairwise Comparison</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.95 (0.77, 1.16)</td>
<td></td>
<td>0.80 (0.66, 0.97)</td>
</tr>
</tbody>
</table>

Source: created by reviewer.

6.4. Subgroup Analyses

Analyses of the primary APTC endpoint were conducted for specific subgroups defined by baseline demographic characteristics and cardiovascular risk factors, using both the ITT (on study through 30 months) and the MITT (on treatment + 30 days) analyses. Estimated hazard ratios and their corresponding nominal 95% confidence intervals were calculated with no correction for multiple comparisons. Therefore, all subgroup analyses presented in this section are considered exploratory. All subgroup analyses in this document were conducted in the ITT.
population using the on-study through 30 months censoring scheme. Similar results were obtained for subgroup analyses based on the on treatment + 30 days censoring scheme for the MITT population and are not discussed further in this document.

In the ITT population, 11065 randomized subjects (45.9%) reported using low dose aspirin for cardio-protection at baseline. Baseline usage rates of low dose aspirin were similar across the 3 treatment groups. The percentage of subjects who experienced APTC events during the trial by 30 months was higher among subjects who took aspirin at baseline (3.0%) than among those who did not (2.2%). The estimated hazard ratios of APTC associated with each treatment comparison were similar for subgroups with or without baseline usage of aspirin. No significant treatment-by-subgroup interactions were observed for any pairwise comparison (Table 10, Figure 5 and Figure 6).

Table 10: Analysis of APTC by Baseline Use of Low Dose Aspirin (ITT, on study through 30 months)

<table>
<thead>
<tr>
<th>Aspirin Use at Baseline</th>
<th>Celecoxib N= 8072</th>
<th>Ibuprofen N= 8040</th>
<th>Naproxen N= 7969</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes: #APTC / N (%)</td>
<td>107/3701 (2.9%)</td>
<td>116/3712 (3.1%)</td>
<td>104/3652 (2.9%)</td>
</tr>
<tr>
<td>Pairwise Comparison HR (95% CI) *</td>
<td>C vs. I 0.93 (0.71, 1.21)</td>
<td>C vs. N 1.02 (0.78, 1.34)</td>
<td></td>
</tr>
<tr>
<td>No: #APTC / N (%)</td>
<td>81/4371 (1.9%)</td>
<td>102/4328 (2.4%)</td>
<td>97/4317 (2.3%)</td>
</tr>
<tr>
<td>Pairwise Comparison HR (95% CI) *</td>
<td>C vs. I 0.78 (0.58, 1.04)</td>
<td>C vs. N 0.83 (0.61, 1.11)</td>
<td></td>
</tr>
</tbody>
</table>

*: Hazard ratios were estimated based upon a Cox model with a fixed effect for treatment while adjusted for region and type of arthritis.
Source: created by reviewer.
The forest plots in Figure 5 (celecoxib vs. naproxen) and Figure 6 (celecoxib vs. ibuprofen) show that the analysis results of the primary composite outcome remained consistent among specific subgroups defined by age, gender, race, region of randomization, type of arthritis, established CVD at baseline, diabetes at baseline, and baseline smoking status. The estimated hazard ratios of APTC and their associated 95% confidence intervals shown in these plots were calculated within each subgroup using a Cox model with treatment as the only covariate.

Figure 5: Forest Plot of Hazard Ratios (Celecoxib vs. Naproxen) for APTC by Specific Subgroups
(ITT, on study through 30 months)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Celecoxib</th>
<th>Naproxen</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>188 / 8072</td>
<td>201 / 7969</td>
<td>0.93 (0.76, 1.13)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>96 / 5175</td>
<td>95 / 5096</td>
<td>1 (0.75, 1.33)</td>
</tr>
<tr>
<td>Male</td>
<td>92 / 2897</td>
<td>106 / 2873</td>
<td>0.86 (0.65, 1.14)</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>92 / 4500</td>
<td>91 / 4320</td>
<td>0.98 (0.73, 1.31)</td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>96 / 3572</td>
<td>110 / 3649</td>
<td>0.89 (0.68, 1.17)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>150 / 6058</td>
<td>157 / 5926</td>
<td>0.94 (0.75, 1.18)</td>
</tr>
<tr>
<td>Other</td>
<td>38 / 2013</td>
<td>44 / 2043</td>
<td>0.86 (0.56, 1.33)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>164 / 6380</td>
<td>166 / 6276</td>
<td>0.98 (0.79, 1.22)</td>
</tr>
<tr>
<td>non-US</td>
<td>24 / 1692</td>
<td>35 / 1693</td>
<td>0.67 (0.4, 1.12)</td>
</tr>
<tr>
<td>Type of Arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>162 / 7259</td>
<td>173 / 7178</td>
<td>0.93 (0.75, 1.15)</td>
</tr>
<tr>
<td>RA</td>
<td>26 / 813</td>
<td>28 / 791</td>
<td>0.9 (0.53, 1.53)</td>
</tr>
<tr>
<td>Baseline CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83 / 1863</td>
<td>90 / 1783</td>
<td>0.88 (0.65, 1.18)</td>
</tr>
<tr>
<td>No</td>
<td>105 / 6209</td>
<td>111 / 5186</td>
<td>0.95 (0.72, 1.24)</td>
</tr>
<tr>
<td>Diabetes at Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80 / 2842</td>
<td>88 / 2765</td>
<td>0.88 (0.65, 1.19)</td>
</tr>
<tr>
<td>No</td>
<td>100 / 5147</td>
<td>113 / 5124</td>
<td>0.95 (0.73, 1.24)</td>
</tr>
<tr>
<td>Baseline Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>54 / 3647</td>
<td>66 / 3657</td>
<td>0.82 (0.57, 1.17)</td>
</tr>
<tr>
<td>Current</td>
<td>55 / 1689</td>
<td>55 / 1631</td>
<td>0.96 (0.66, 1.4)</td>
</tr>
<tr>
<td>Previous</td>
<td>78 / 2729</td>
<td>79 / 2674</td>
<td>0.88 (0.72, 1.34)</td>
</tr>
</tbody>
</table>

Source: created by reviewer.
Figure 6: Forest Plot of Hazard Ratios (Celecoxib vs. Ibuprofen) for APTC by Specific Subgroups (ITT, on study through 30 months)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>188/8072</td>
<td>218/8040</td>
<td>0.86 (0.7, 1.04)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>96/5175</td>
<td>108/5174</td>
<td>0.88 (0.67, 1.16)</td>
</tr>
<tr>
<td>Male</td>
<td>92/2897</td>
<td>110/2866</td>
<td>0.83 (0.63, 1.09)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>92/4500</td>
<td>94/4341</td>
<td>0.94 (0.7, 1.25)</td>
</tr>
<tr>
<td>&gt;= 65</td>
<td>96/3572</td>
<td>124/3699</td>
<td>0.79 (0.61, 1.03)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>150/6058</td>
<td>166/5991</td>
<td>0.89 (0.72, 1.11)</td>
</tr>
<tr>
<td>Other</td>
<td>38/2013</td>
<td>52/2048</td>
<td>0.72 (0.47, 1.1)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>164/6380</td>
<td>179/6352</td>
<td>0.91 (0.73, 1.12)</td>
</tr>
<tr>
<td>non-US</td>
<td>24/1692</td>
<td>39/1688</td>
<td>0.6 (0.36, 1.01)</td>
</tr>
<tr>
<td><strong>Type of Arthritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>162/7259</td>
<td>190/7208</td>
<td>0.84 (0.68, 1.04)</td>
</tr>
<tr>
<td>RA</td>
<td>26/813</td>
<td>28/832</td>
<td>0.94 (0.55, 1.6)</td>
</tr>
<tr>
<td><strong>Baseline CVD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83/1863</td>
<td>99/1834</td>
<td>0.81 (0.6, 1.09)</td>
</tr>
<tr>
<td>No</td>
<td>105/6209</td>
<td>119/6206</td>
<td>0.88 (0.68, 1.14)</td>
</tr>
<tr>
<td><strong>Diabetes at Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80/2842</td>
<td>84/2884</td>
<td>0.96 (0.71, 1.3)</td>
</tr>
<tr>
<td>No</td>
<td>108/5147</td>
<td>133/5076</td>
<td>0.79 (0.62, 1.02)</td>
</tr>
<tr>
<td><strong>Baseline Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>54/3647</td>
<td>85/3652</td>
<td>0.63 (0.45, 0.89)</td>
</tr>
<tr>
<td>Current</td>
<td>55/1689</td>
<td>57/1680</td>
<td>0.95 (0.66, 1.38)</td>
</tr>
<tr>
<td>Previous</td>
<td>78/2729</td>
<td>75/2699</td>
<td>1.01 (0.74, 1.39)</td>
</tr>
</tbody>
</table>

Source: created by reviewer.
6.5 Summary of Findings

PRECISION was a large-scale cardiovascular safety trial which randomized a total of 24,081 subjects with osteoarthritis or rheumatoid arthritis requiring a chronic analgesic regimen. The trial had an average follow up of 34.3 months and a mean treatment exposure of 20.4 months. Of the 24,081 randomized subjects, 70% were followed until the planned study end and 80% were followed until at least 30 months. The pre-specified primary analyses were an “ITT analysis” based upon a Cox proportional hazards model utilizing an “on-study” censoring strategy for the primary composite CV endpoint APTC, and a “MITT analysis” utilizing an “on-treatment + 30 days” censoring strategy for APTC. The results of the primary analyses ruled out the pre-specified margins (33% risk increase for the “ITT analysis” and 40% risk increase for the “MITT analysis”, respectively), and therefore showed no evidence of excess risk of APTC associated with the use of celecoxib 100-200mg twice a day compared to both naproxen 375-500mg twice a day and ibuprofen 600-800mg three times daily.

Analyses of the individual components of APTC, i.e., non-fatal stroke, non-fatal MI, and CV death, were consistent with the primary analysis. Analysis results for APTC remained consistent across various subgroups including age, gender, race, region, arthritis type, established CVD, baseline diabetes, and subjects with or without low-dose aspirin use for CV protection at baseline. Time-to-event analyses for two other CV-related endpoints, MACE and all-cause mortality, showed consistent results with that of the primary APTC endpoint.

The overall rate of study discontinuation in PRECISION was 29.2%. This review discussed sensitivity analyses to evaluate the impact of high study withdrawal on the estimated hazard ratios of APTC. The results of the sensitivity analysis considering potential informative censoring in subjects who discontinued study prematurely did not alter the conclusion of non-excessive risk for celecoxib relative to either naproxen or ibuprofen. A tipping point analysis showed that unobserved events that could have occurred in these subjects after they withdrew from the trial were unlikely to change the conclusions of the trial, unless the rate of APTC among these subjects was much higher (3 times higher) in the celecoxib arm. This scenario appears unlikely because the rate of and reasons for study withdrawal were similar in all three treatment arms in PRECISION.
7 Epidemiology Summary

Division of Epidemiology II (DEPI) reviewed the epidemiology studies published since the last review was completed on this topic in 2013. DAAAP requested that only studies that advance the current understanding of the risk of CV thrombotic events associated with NSAID use be included in the literature search. DEPI focused the current literature review on the same questions that were the focus of the 2013 literature review:

1. Are there data to better refine the understanding of time to event for cardiovascular risk (including stroke) with NSAIDs? Early hazard versus increased risk with cumulative use (or both, depending on the population)?
2. Describe any data that suggest specific vulnerable populations (e.g., history of MI, CV risk factors, post-operative coronary artery bypass graft [CABG] or others) for NSAID-associated CV risk (including stroke)
3. Does use of NSAIDs in patients with history of MI increase the risk of recurrent MI or death?
4. Are there data to support differential CV risk (including stroke) across the specific NSAIDs?

The DEPI search of National Library of Medicine’s PubMed database was conducted on January 24, 2018. The search strategy is described in detail in the DEPI memo. Using search strings for non-steroidal anti-inflammatory agents and the targeted thrombotic CV adverse outcomes, DEPI identified 2,389 English language articles published from 12/04/2012 to 1/24/2018. The exclusion criteria were:

- Publications that did not report on a research study (e.g. commentaries and reviews)
- Animal studies, cellular studies, pharmacokinetic studies, pharmacodynamics studies
- Non-observational studies (e.g. randomized control trials, case reports, case series)
- Meta-analysis, cross-sectional studies, or studies that only conducted descriptive analyses
- Studies that did not address the four target questions
- Studies that did not include thrombotic CV events as a primary outcome
- Studies that were included in previous DEPI review or that used the same data as the publications included in previous review

DEPI identified 12 potential observational studies that evaluated the risk of CV thrombotic events associated with NSAID use.27,28,29,30,31,32,33,34,35,36,37,38 The 12 publications included

four cohort studies,\textsuperscript{32,35,36,37} six case-control studies,\textsuperscript{27,29,30,31,33,38} and three self-controlled studies\textsuperscript{28,34,37} conducted in eight non-U.S. countries\textsuperscript{39} that met the PubMed search criteria. Eight studies were based on administrative claims data from nationwide health insurance plans,\textsuperscript{27,28,29,31,32,34,35,37} one was based on prospectively collected patient registry data,\textsuperscript{36} and three were based on a primary healthcare provider database.\textsuperscript{30,33,38} DEPI further evaluated the quality of these studies based on whether their findings could be used to support additional labeling changes with regard to a differential CV risk between NSAIDS, vulnerable populations, risk factors, or time to event..

**Differential CV risk between NSAID products**

To support labeling recommendations regarding a differential CV risk between NSAID products, DEPI looked for evidence from “head-to-head comparisons between NSAIDs that were adequately powered and able to adjust for differences in severity of underlying illness as well as in NSAID dose.” –a criterion in Dr. Staffa’s memo.

Among the 12 identified studies, 11\textsuperscript{40} attempted to address whether a differential CV risk exists between NSAID products,\textsuperscript{27,29,30,31,32,33,34,35,36,37,38} The evaluation of the 11 studies based on the DEPI criterion is summarized below and in Table 1:

- Nine of the 11 identified studies that examined CV risk by NSAID products used “non-users” or “non-current users” as comparators,\textsuperscript{27,29,30,31,32,33,35,37,38} and only one of the nine studies accounted for NSAID dose in the analyses.\textsuperscript{27} Confounding by the severity of NSAID indication or NSAID dose, or both, remain a concern for the nine studies.

39 Denmark (N=3), Taiwan (N=3), Spain (N=2), Germany, Japan, Korea, United Kingdom, Canada.
40 One of the 11 studies (by Fosbol et al.) approached the research question with two study designs: a cohort design (with non-user comparator) and a self-control design.
Two studies used a self-controlled design,\textsuperscript{34,37} and one study, conducted in a population of patients with osteoarthritis or rheumatoid arthritis, compared patients who were prescribed celecoxib to patients prescribed “all other (non-celecoxib) NSAIDs”.\textsuperscript{36} While using patients as their own comparison and the restriction to treated patients with same indication for NSAIDs both could reduce the concern of confounding by NSAID indications, the three studies did not adjust for NSAID dose. Thus, confounding by NSAID dose is still a concern.

None of the studies reported \textit{a priori} calculations to support sufficient power to derive precise effect estimates for any of the studied NSAIDs.

Therefore, DEPI determined that none of these studies can provide quality data to inform whether there is differential CV risk across NSAIDs.
Table 1. Summary of design issues of the identified studies reported CV risks by NSAIDs

<table>
<thead>
<tr>
<th>Reference; Author</th>
<th>Study design</th>
<th>Reference group</th>
<th>Accounted/adjusted for the severity of NSAID indication</th>
<th>Accounted/adjusted for NSAID dose</th>
<th>Report a priori power calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bally et al., 2018</td>
<td>Nested case-control</td>
<td>Non-use of studied NSAIDs</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thone et al., 2017</td>
<td>Nested case-control</td>
<td>Past use of studied NSAIDs (≥ 184 days prior to the index date)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dalal et al., 2017</td>
<td>Nested case-control</td>
<td>Remote use of studied NSAIDs (between 60 days and 1 year prior to index date)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Wu et al., 2016</td>
<td>Case-control</td>
<td>Non-use of studied NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kim et al., 2015</td>
<td>Cohort</td>
<td>Non-users of studied NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Garcia-Poza et al., 2015</td>
<td>Case-control</td>
<td>Non-use of NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Chuang et al., 2015</td>
<td>Case-crossover</td>
<td>Self-control</td>
<td>Maybe (by using individual patients as their own control)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lindhardsen et al., 2014</td>
<td>Cohort</td>
<td>Non-users of studied NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hirayama et al., 2014</td>
<td>Cohort</td>
<td>Users of other (i.e. non-celecoxib) studied NSAIDs</td>
<td>Maybe (by restricting to osteoarthritis or rheumatoid arthritis patients who were treated with NSAIDs)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fosbol et al., 2014</td>
<td>Cohort</td>
<td>Non-users of studied NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fosbol et al., 2015</td>
<td>Case-crossover</td>
<td>Self-control</td>
<td>Maybe (by using individual patients as their own control)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>de Abajo et al., 2014</td>
<td>Case-control</td>
<td>Non-use of studied NSAID</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Vulnerable population or risk factors

DEPI identified one study of NSAIDs and CV risk in a vulnerable population. A case-crossover study reported that NSAID use during acute respiratory infection (ARI) episodes is associated with higher increased risk of MI, compared to NSAID use alone, or having ARI episode without NSAID use (relative to no exposure to NSAIDs or ARI).\textsuperscript{28} However, the study was based on claims data, which are unable to capture the severity of ARI. NSAIDs might have been prescribed to patients who have more severe ARI. Given that ARI is also a risk factor for MI,\textsuperscript{41,42,43} the higher observed risk among NSAID use during ARI episodes could be due to the confounding by ARI severity.

Consequently, DEPI does not recommend changing the label language on vulnerable populations or risk factors based on this one study.

Time to event of NSAID associated CV risk

The current NSAID class label carries the warning that the increased risk of serious CV thrombotic events can begin as early as the first weeks of NSAID treatment, based on observational studies identified in DEPI’s previous literature review and recommendations from the 2014 advisory committees.\textsuperscript{44} It is less clear if the risk would increase by the length of NSAID treatment. From the current literature search, DEPI identified one nested case-control study that explored the temporal relationship between NSAID exposure and acute MI risk.\textsuperscript{27} The study was the first to use an advanced analytical method (i.e. the Weighted Cumulative Exposure, WCE) to simultaneously account for dose and timing of past exposure when characterizing NSAID-associated CV risk. The findings confirmed that current, and very recent exposure of all NSAIDs had the greatest impact on MI risk. The authors speculated some NSAIDs might be safer than others, given that the duration of the exposure prior to a statistically significant increased MI risk varied among the NSAIDs. Despite some strengths of this approach, the reference group in the study was “non-users,” and no formal statistical tests were performed comparing the NSAIDs head-to-head. DEPI disagrees that the study provided evidence that an increased CV risk is different between NSAIDs, based on duration or exposure prior to an event. Furthermore, while the study modeled the association between NSAIDs and MI risk up to 90 days of exposure, it did not characterize NSAID-related CV risk beyond 90 days of exposure.

Therefore, DEPI does not recommend changing the label regarding the time to event of NSAID-associated CV thrombotic event.

\textsuperscript{44} \url{https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm}
Conclusions

The observational studies published after the DEPI literature review completed in 2013 do not advance our current knowledge on thrombotic CV event risk associated with NSAID use. They do not meet the criteria laid out in the 2015 DEPI Director memo—using “head-to-head” comparisons among NSAIDs, adequately powered and able to adjust for differences in severity of underlying illness as well as in NSAID dose. Therefore, DEPI does not recommend additional labeling changes regarding differential CV risk between products, vulnerable populations, risk factors, or time to event based on the observational studies published since the DEPI literature review completed in 2013.
8 Drug Utilization Summary

8.1 Methods

Proprietary drug utilization databases available to FDA were used to conduct this analysis. Detailed descriptions of the databases are included in Section 8.4. Time periods analyzed varied based on availability of data across the disparate data sources.

8.1.1 Data Sources Used

The IQVIA™ National Sales Perspective (NSP) database was used to determine settings of care based on the volume of celecoxib, ibuprofen and naproxen single ingredient products (prescription and OTC) sold from U.S. manufacturers to various channels of distribution in 2017.

The IQVIA™ National Prescription Audit (NPA) database was used to obtain the nationally estimated number of prescriptions dispensed from 2006 through 2017 and the IQVIA™ Total Patient Tracker (TPT) database was used to obtain the nationally estimated number of patients who received a dispensed prescription from 2013 through 2017 for celecoxib, ibuprofen or naproxen single ingredient products from U.S. outpatient retail pharmacies.

The OTC Ingredient Level Report (ILR) was used to obtain the nationally estimated number of OTC packages sold for ibuprofen and naproxen single ingredient products to consumers from U.S. retail store outlets from 2012 through 2016.

The OTC Consumer and Shopper Insights Advantage (CSIA) database was used to obtain the nationally estimated number of households who purchased OTC ibuprofen or naproxen single ingredient products in the U.S. from 2016 through 2017. The estimated number of households was stratified by the age of the head of household (reported primary purchaser for the household) by age groups 18-64 years and 65 years or older.

The Syneos Health Research and Insights TreatmentAnswers™, a U.S. office-based physician survey database, was used to obtain the top diagnoses associated with the use of celecoxib, ibuprofen, and naproxen single ingredient products (prescription or OTC) mentioned during an office visit from 2016 through 2017, aggregated. Diagnoses data by the number of drug use mentions\(^45\) were captured based on International Classification of Diseases, Tenth Revisions, Clinical Modification (ICD-10-CM) codes with 95% confidence intervals.

8.2 Results

8.2.1 Settings of Care

Manufacturer sales data for 2017 indicated that approximately 84% of celecoxib products were sold to U.S. retail pharmacies, followed by 9% to non-retail settings, and 7% to mail order

\(^{45}\) The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
Similarly, 71% of ibuprofen and naproxen single ingredient products (prescription and OTC) were sold to retail pharmacies, followed by 28% to non-retail settings, and 1% to mail order pharmacies. Accordingly, we focused our analysis only on the retail settings. Utilization data from other settings, such as hospitals, were not included in this analysis.

8.2.2 Dispensed Prescription Data

8.2.2.1 Prescription-Level Data from U.S. Outpatient Retail Pharmacies

Figure 1 below and Table 1 in Section 8.5 provide the nationally estimated number of prescriptions dispensed for celecoxib, ibuprofen, and naproxen single ingredient products from U.S. outpatient retail pharmacies from 2006 through 2017. An estimated 70 million total prescriptions were dispensed for the select NSAIDs in 2017. Among the NSAIDs, ibuprofen single ingredient products accounted for the largest proportion of use at 64% (44.8 million prescriptions), followed by naproxen single ingredient products at 26% (18 million prescriptions) and celecoxib at 10% (7.3 million prescriptions) of total prescriptions in 2017.

Over the last twelve years, prescription utilization for ibuprofen single ingredient products increased 60% from 28 million prescriptions in 2006 to 44.8 million prescriptions in 2017. Prescriptions dispensed for naproxen single ingredient products also increased 10% from 16.4 million prescriptions in 2006 to 18 million prescriptions in 2017. Meanwhile, the utilization of celecoxib decreased 34% from 11 million prescriptions in 2006 to 7.3 million prescriptions in 2017 (Figure 1).


47 Sales data for ibuprofen, and naproxen single ingredient products were combined to determine the settings of care for these products. IQVIA™ National Sales Perspectives Database. Year 2017. Extracted March 2017. File: NSP 2017-1972 Celecoxib, Ibuprofen, Naproxen by Sup Ch 3-5-2018
8.2.2.2 Patient Level Data from U.S. Outpatient Retail Pharmacies

Figure 2 below and Table 2 in Section 8.5 provide the nationally estimated number of patients who received a dispensed prescription for celecoxib, ibuprofen or naproxen single ingredient products from U.S. outpatient retail pharmacies, stratified by age groups from 2013 through 2017. An estimated 38.3 million total patients received a dispensed prescription for the select NSAIDs in year 2017. Among the NSAIDs, the largest proportion of patients received ibuprofen single ingredient products, accounting for 72% (27.5 million patients), followed by naproxen single ingredient products at 28% (10.7 million patients) and celecoxib at 6% (2.2 million patients) of total patients in 2017. Of note, patients may have received more than one product during a given year due to switching or other reasons.

Utilization by age showed that the largest proportion of use for ibuprofen single ingredient products was among patients aged 25-44 years, accounting for approximately 34% of ibuprofen patients. For the other two NSAIDs, the largest proportion of use was among patients aged 45-64 years, accounting for 37% of naproxen patients and 44% of celecoxib patients in 2017.
Figure 2

Nationally estimated number of patients who received a dispensed prescription for celecoxib, ibuprofen, or naproxen single ingredient products from U.S. outpatient retail pharmacies, stratified by patient age groups, 2013 through 2017


Unique patient counts may not be added across time periods or products due to the possibility of double counting those patients who may have received multiple treatments during the study period.

8.2.3 Over the Counter Sales Data

8.2.3.1 Over the Counter Sales Data from U.S. Retail Store Outlets

Table 3 in Section 8.5 provides the nationally estimated number of OTC packages sold for ibuprofen and naproxen single ingredient products to consumers from U.S. retail stores from 2012 through 2016. An estimated 172.6 million packages of OTC ibuprofen single ingredient products and 64 million packages of OTC naproxen single ingredient products were sold in 2016. Sales appeared to remain relatively steady over the five-year time frame.

8.2.3.2 Household Purchasing Data of Over the Counter Products

Table 4 in Section 8.5 provides the nationally estimated number of households who purchased OTC ibuprofen or naproxen single-ingredient products in the U.S., stratified by the age of the head of household from 2016 through 2017. An estimated 63.2 million households purchased OTC ibuprofen single ingredient products and 26 million households purchased OTC naproxen single ingredient products in 2017. Head of households aged 18-64 years accounted for the highest proportion of households who purchased these OTC NSAIDs.
8.2.4 Diagnoses Data from U.S. Office Based Physician Surveys

Table 5 in Section 8.5 provides the top three diagnoses (ICD-10-CM) associated with the use of celecoxib, ibuprofen, and naproxen single ingredient products by drug use mentions as reported by U.S. office-based physician surveys, stratified by age groups from 2016 through 2017, aggregated. During the examined time frame, the top diagnoses reported in association with ibuprofen single ingredient products was fever unspecified in patients 0-24 years, low back pain in patients aged 25-44 and 45-64 years, and encounter for follow-up exam after treatment among patients aged 65 years or older. For naproxen single ingredient products, the top diagnoses reported was chondromalacia patellae unspecified knee in patients aged 0-24 years, low back pain in patients aged 25-44 and 45-64 years, and osteoarthritis unspecified site among patients aged 65 years or older. For celecoxib products, the top diagnoses reported was carpal tunnel syndrome in patients aged 0-24 years, vasectomy status in patients aged 25-44 years, and osteoarthritis unspecified site among patients 45 years or older.

8.3 Limitations

The drug utilization findings should be interpreted in the context of the known limitations of the databases used. This analysis focused on retail settings; therefore, the utilization data reported in this analysis can only be generalized to these settings of care and may not apply to other settings in which these products may be prescribed or dispensed such as mail-order pharmacies, non-retail settings, or online purchasing. The IQVIA™ NPA and TPT dispensed prescription and patient data capture retail prescription activity; utilization data for OTC products are captured in these databases only when prescriptions are filled and dispensed at the pharmacy. Thus, data on OTC ibuprofen or naproxen single ingredient products purchased by consumers without a prescription is not provided in this database.

OTC products sales are provided from the OTC Ingredient Level Report which provides retail purchases by consumers of OTC products in a sample of nearly 106,000 retail drug stores, grocery supermarkets, mass merchandisers, and select club stores (excluding Costco). The OTC CSIA provides purchasing data of OTC products at the household level based on survey and scanner data from a sample of approximately 62,000 households, projected to the U.S. census population. Sales to consumers from convenience stores, specialty stores, internet sales, phone sales, or kiosks are not available in the OTC Ingredient Level Report, whereas the CSIA data can be scans of products purchased anywhere. However, these two OTC databases do not provide information of the individual purchaser, the intended user, or the patient’s actual usage or consumption of OTC products. Due to these limitations, the true extent of use of OTC ibuprofen or naproxen single ingredient products is likely underestimated.

Furthermore, many OTC ibuprofen and naproxen products are combination products, including products marketed for analgesic indications, sleep indication, and cough/cold indications; however, this analysis focused on utilization of ibuprofen and naproxen single ingredient ONLY products.

Lastly, the Syneos™ office-based physician survey data was used to provide insight into prescriber intent for the typical uses for a drug in an office-based physician’s clinical practice. However, the sample of office-based physicians may not represent the care from other specialty offices, such as dental offices, where prescribing for NSAIDs products may have occurred.
8.4 Drug Utilization Database Descriptions

**IQVIA™ National Sales Perspectives (NSP)**

The IQVIA™ National Sales Perspectives™ (NSP) measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

**IQVIA™ National Prescription Audit (NPA)**

The IQVIA™ National Prescription Audit (NPA) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 59,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 93% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 – 75% (varies by class and geography) of mail service pharmacies and approximately 71 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

**IQVIA™ Total Patient Tracker (TPT)**

The IQVIA™ Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 93% coverage and a sample of ~59,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.
**OTC Ingredient Level Report (ILR)**

The OTC Ingredient Level Report captures weekly POS sales from other 65,000 retailer stores and applies proprietary projection weighting schemes and complementary observational causal related data (instore displays and feature advertisements) to report overall sales from multiple channels representing nearly 106,000 stores and over $1.3 trillion in annual US sales. The channels included are: Grocery Supermarkets, Drug stores, Mass Merchandiser stores, Club stores, Dollar stores and DeCa Military commissaries.

**OTC Consumer and Shopper Insights Advantage™ (CSIA)**

The Consumer and Shopper Insights Advantage™ (CSIA) is a web-based application that provides users with immediate access to household panel purchase data for the latest 4 years (and the last 4 calendar years), as well as demographics of shoppers and product buyers, and prevalence of six major medical conditions for those households for the latest 2 years. The panel data draws from the Consumer Network of approximately 100,000 active households (62,000 households meeting 1-year reporting requirements) who record their CPG purchases on an ongoing basis. CSIA is fueled by the weekly, transaction-level purchase records to provide projected household purchase data using pre-defined, customizable report templates and full ad-hoc reporting capabilities. Purchase data are included for health care categories down to the brand level. Purchase metrics include % of household buying, buying rate ($/volume/units per buyer), frequency of purchase and other standard measures. Demographics cover income levels, education, age, and nearly all other major demographics attributes. The presence of six prevalent medical conditions (high cholesterol; high blood pressure; obesity; diabetes; heart attack; and stroke) is captured through an annual survey of the CN panel. Aggregate information on these conditions is in the CSIA interface. All data are projected nationally, to U.S. census regions and divisions, and markets for all retail venues reported by panelists including Food, Drug, Mass Merchandiser/Supercenter, Club stores, Dollars stores and other Specialty outlets.

**Syneos Health Research & Insights TreatmentAnswers™**

The Syneos Health Research & Insights TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Table 3
Nationally estimated number of OTC packages sold for ibuprofen and naproxen single ingredient products to consumers from U.S. retail store outlets*, 2012 through 2016

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
<th>Share</th>
<th>2013</th>
<th>Share</th>
<th>2014</th>
<th>Share</th>
<th>2015</th>
<th>Share</th>
<th>2016</th>
<th>Share</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Packages N</td>
<td>%</td>
<td>Packages N</td>
<td>%</td>
<td>Packages N</td>
<td>%</td>
<td>Packages N</td>
<td>%</td>
<td>Packages N</td>
<td>%</td>
</tr>
<tr>
<td>Total OTC Packages Sold</td>
<td>235,612,149</td>
<td>100.0%</td>
<td>234,705,710</td>
<td>100.0%</td>
<td>236,171,160</td>
<td>100.0%</td>
<td>236,911,323</td>
<td>100.0%</td>
<td>236,682,102</td>
<td>100.0%</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>173,865,086</td>
<td>73.8%</td>
<td>174,589,736</td>
<td>74.4%</td>
<td>172,110,722</td>
<td>72.9%</td>
<td>171,840,875</td>
<td>72.5%</td>
<td>172,634,198</td>
<td>72.9%</td>
</tr>
<tr>
<td>Naproxen</td>
<td>61,747,063</td>
<td>26.2%</td>
<td>60,115,974</td>
<td>25.6%</td>
<td>64,060,438</td>
<td>27.1%</td>
<td>65,070,448</td>
<td>27.5%</td>
<td>64,047,904</td>
<td>27.1%</td>
</tr>
</tbody>
</table>


*Retail store outlets includes consumer purchases from pharmacies in drug stores, grocery supermarkets, mass merchandiser stores, and select club stores. Specialty stores, convenience stores, internet sales, phone sales, and kiosks are not included.

Table 4
Nationally estimated number of households who purchased OTC ibuprofen and naproxen single-ingredient products in the U.S. stratified by the age of the head of household, 2016 through 2017

<table>
<thead>
<tr>
<th></th>
<th>2016</th>
<th>Share</th>
<th>2017</th>
<th>Share</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Households N</td>
<td>%</td>
<td>Households N</td>
<td>%</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>64,004,879</td>
<td>100.0%</td>
<td>63,180,917</td>
<td>100.0%</td>
</tr>
<tr>
<td>18-64 years</td>
<td>50,095,372</td>
<td>78.3%</td>
<td>49,806,801</td>
<td>78.8%</td>
</tr>
<tr>
<td>65 years or older</td>
<td>13,909,507</td>
<td>21.7%</td>
<td>13,374,116</td>
<td>21.2%</td>
</tr>
<tr>
<td>Naproxen</td>
<td>27,390,279</td>
<td>100.0%</td>
<td>25,980,947</td>
<td>100.0%</td>
</tr>
<tr>
<td>18-64 years</td>
<td>19,656,201</td>
<td>71.8%</td>
<td>18,629,258</td>
<td>71.7%</td>
</tr>
<tr>
<td>65 years or older</td>
<td>7,734,078</td>
<td>28.2%</td>
<td>7,351,689</td>
<td>28.3%</td>
</tr>
</tbody>
</table>


The head of household age counts may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. Households may have also purchased more than one drug product during the study period. Therefore, summing across age groups or drug products is not advisable and will result in overestimates of households.
### Table 5
Top diagnoses associated with the use of celecoxib, ibuprofen, or naproxen single ingredient products as reported by U.S. office-based physician surveys from January 2016 through December 2017, aggregated

<table>
<thead>
<tr>
<th>Diagnosis Description</th>
<th>January 2016 through December 2017</th>
<th>Uses N</th>
<th>Share %</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL USES</strong></td>
<td></td>
<td>134,664,000</td>
<td>100.0%</td>
<td>132,495,000 - 136,832,000</td>
</tr>
<tr>
<td><strong>Ibuprofen</strong></td>
<td></td>
<td>84,640,000</td>
<td>62.9%</td>
<td>82,921,000 - 86,359,000</td>
</tr>
<tr>
<td><strong>0-24 years</strong></td>
<td></td>
<td>36,158,000</td>
<td>43.0%</td>
<td>35,231,000 - 35,885,000</td>
</tr>
<tr>
<td>R05 Fever, unspecified</td>
<td></td>
<td>8,324,000</td>
<td>22.9%</td>
<td>7,785,000 - 8,863,000</td>
</tr>
<tr>
<td>J029 Acute pharyngitis, unspecified</td>
<td></td>
<td>2,346,000</td>
<td>6.5%</td>
<td>2,060,000 - 2,632,000</td>
</tr>
<tr>
<td>S93490A Sprain of unspecified ankle, initial encounter</td>
<td></td>
<td>1,270,000</td>
<td>3.5%</td>
<td>1,059,000 - 1,480,000</td>
</tr>
<tr>
<td>All Others</td>
<td></td>
<td>24,418,000</td>
<td>67.2%</td>
<td>23,495,000 - 25,341,000</td>
</tr>
<tr>
<td><strong>25-44 years</strong></td>
<td></td>
<td>22,804,000</td>
<td>26.9%</td>
<td>21,912,000 - 23,697,000</td>
</tr>
<tr>
<td>M545 Low back pain</td>
<td></td>
<td>1,277,000</td>
<td>5.6%</td>
<td>1,066,000 - 1,488,000</td>
</tr>
<tr>
<td>Z09 Encnt for u/e exam afttnt for cond oth than malig neopl</td>
<td></td>
<td>984,000</td>
<td>4.3%</td>
<td>798,000 - 1,169,000</td>
</tr>
<tr>
<td>S134XXA Sprain of ligaments of cervical spine, initial encounter</td>
<td></td>
<td>773,000</td>
<td>3.4%</td>
<td>609,000 - 938,000</td>
</tr>
<tr>
<td>All Others</td>
<td></td>
<td>19,770,000</td>
<td>86.7%</td>
<td>18,939,000 - 20,601,000</td>
</tr>
<tr>
<td><strong>45-64 years</strong></td>
<td></td>
<td>17,711,000</td>
<td>21.0%</td>
<td>16,983,000 - 18,559,000</td>
</tr>
<tr>
<td>M545 Low back pain</td>
<td></td>
<td>1,247,000</td>
<td>7.0%</td>
<td>1,038,000 - 1,456,000</td>
</tr>
<tr>
<td>Z09 Encnt for u/e exam afttnt for cond oth than malig neopl</td>
<td></td>
<td>1,009,000</td>
<td>5.7%</td>
<td>821,000 - 1,196,000</td>
</tr>
<tr>
<td>S134XXA Sprain of ligaments of cervical spine, initial encounter</td>
<td></td>
<td>463,000</td>
<td>2.6%</td>
<td>336,000 - 590,000</td>
</tr>
<tr>
<td>All Others</td>
<td></td>
<td>15,052,000</td>
<td>84.7%</td>
<td>14,327,000 - 15,777,000</td>
</tr>
<tr>
<td><strong>65 years or older</strong></td>
<td></td>
<td>6,223,000</td>
<td>7.4%</td>
<td>5,757,000 - 6,689,000</td>
</tr>
<tr>
<td>M545 Low back pain</td>
<td></td>
<td>1,180,000</td>
<td>7.5%</td>
<td>977,000 - 1,380,000</td>
</tr>
<tr>
<td>Z09 Encnt for u/e exam afttnt for cond oth than malig neopl</td>
<td></td>
<td>1,009,000</td>
<td>5.7%</td>
<td>798,000 - 1,169,000</td>
</tr>
<tr>
<td>S134XXA Sprain of ligaments of cervical spine, initial encounter</td>
<td></td>
<td>463,000</td>
<td>2.6%</td>
<td>336,000 - 590,000</td>
</tr>
<tr>
<td>All Others</td>
<td></td>
<td>15,052,000</td>
<td>84.7%</td>
<td>14,327,000 - 15,777,000</td>
</tr>
<tr>
<td><strong>Unspecified Age</strong></td>
<td></td>
<td>39,394,000</td>
<td>29.3%</td>
<td>38,221,000 - 40,567,000</td>
</tr>
<tr>
<td><strong>Celecoxib</strong></td>
<td></td>
<td>10,630,000</td>
<td>7.9%</td>
<td>10,021,000 - 11,240,000</td>
</tr>
<tr>
<td><strong>0-24 years</strong></td>
<td></td>
<td>88,000</td>
<td>0.8%</td>
<td>32,000 - 143,000</td>
</tr>
<tr>
<td>G5600 Carpal tunnel syndrome, unspecified upper limb</td>
<td></td>
<td>15,000</td>
<td>17.1%</td>
<td>&lt;500 - 38,000</td>
</tr>
<tr>
<td>M940 Chondrocostal junction syndrome [Tietze]</td>
<td></td>
<td>15,000</td>
<td>16.8%</td>
<td>&lt;500 - 38,000</td>
</tr>
<tr>
<td>M7661 Achilles tendinitis, right leg</td>
<td></td>
<td>15,000</td>
<td>16.7%</td>
<td>&lt;500 - 38,000</td>
</tr>
<tr>
<td>All Others</td>
<td></td>
<td>43,000</td>
<td>49.4%</td>
<td>4,000 - 82,000</td>
</tr>
<tr>
<td><strong>25-44 years</strong></td>
<td></td>
<td>2,272,000</td>
<td>21.4%</td>
<td>1,990,000 - 2,553,000</td>
</tr>
<tr>
<td>Z9852 Vasectomy status</td>
<td></td>
<td>360,000</td>
<td>15.8%</td>
<td>247,000 - 472,000</td>
</tr>
<tr>
<td>M545 Low back pain</td>
<td></td>
<td>171,000</td>
<td>7.5%</td>
<td>94,000 - 249,000</td>
</tr>
<tr>
<td>Z302 Encounter for sterilization</td>
<td></td>
<td>169,000</td>
<td>7.4%</td>
<td>92,000 - 246,000</td>
</tr>
<tr>
<td>All Others</td>
<td></td>
<td>1,572,000</td>
<td>69.2%</td>
<td>1,338,000 - 1,806,000</td>
</tr>
<tr>
<td><strong>45-64 years</strong></td>
<td></td>
<td>4,399,000</td>
<td>41.4%</td>
<td>4,007,000 - 4,791,000</td>
</tr>
<tr>
<td>M1990 Unspecified osteoarthritis, unspecified site</td>
<td></td>
<td>525,000</td>
<td>11.9%</td>
<td>390,000 - 661,000</td>
</tr>
<tr>
<td>M170 Bilateral primary osteoarthritis of knee</td>
<td></td>
<td>356,000</td>
<td>8.1%</td>
<td>244,000 - 483,000</td>
</tr>
<tr>
<td>M179 Osteoarthritis of knee, unspecified</td>
<td></td>
<td>235,000</td>
<td>5.3%</td>
<td>144,000 - 325,000</td>
</tr>
<tr>
<td>All Others</td>
<td></td>
<td>3,283,000</td>
<td>74.6%</td>
<td>2,944,000 - 3,622,000</td>
</tr>
<tr>
<td><strong>65 years or older</strong></td>
<td></td>
<td>3,648,000</td>
<td>34.3%</td>
<td>3,292,000 - 4,005,000</td>
</tr>
<tr>
<td>M1990 Unspecified osteoarthritis, unspecified site</td>
<td></td>
<td>734,000</td>
<td>20.1%</td>
<td>574,000 - 894,000</td>
</tr>
<tr>
<td>M170 Bilateral primary osteoarthritis of knee</td>
<td></td>
<td>363,000</td>
<td>10.0%</td>
<td>250,000 - 476,000</td>
</tr>
<tr>
<td>M179 Osteoarthritis of knee, unspecified</td>
<td></td>
<td>270,000</td>
<td>7.4%</td>
<td>172,000 - 367,000</td>
</tr>
<tr>
<td>All Others</td>
<td></td>
<td>2,282,000</td>
<td>62.5%</td>
<td>1,999,000 - 2,564,000</td>
</tr>
<tr>
<td><strong>Unspecified Age</strong></td>
<td></td>
<td>224,000</td>
<td>2.1%</td>
<td>135,000 - 312,000</td>
</tr>
</tbody>
</table>

Syneos Health Research & Insights Treatment Answers® recommends caution interpreting projected annual uses or mentions below 100,000, as the sample size is very small with correspondingly large confidence intervals.
9 Office of Scientific Investigation Summary

Eight clinical sites were inspected in support of this NDA: 6 were domestic, 2 were foreign sites. The sponsor and the CRO responsible for site management and monitoring were also inspected.

Of the sites chosen for this inspection assignment, two clinical sites also took part in the Ambulatory Blood Pressure Monitoring (ABPM) sub-study. The raw data (individual blood pressure readings) received from the central ABPM reading laboratory, was compared to the ABPM data line listings submitted by the sponsor. No discrepancies were noted - the raw data used to calculate the ABPM sub-study endpoint was verifiable.

Overall, the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of this supplemental NDA.
## Appendix 1 – Summary table – large celecoxib RCTs

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Indication</th>
<th>Study drugs</th>
<th>APTC endpoint n (rate/100pyr) Study drug*</th>
<th>APTC endpoint n (rate/100pyr) Comparator*</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS</td>
<td>RA/OA (median treatment 6-9 months)</td>
<td>celecoxib 400 mg bid (n= 3987) vs. diclofenac 75 mg bid (n=1996) or ibuprofen 800 mg tid (n=1985)</td>
<td>34 (0.9%)</td>
<td>(diclofenac) 15 (0.8%)</td>
<td>(ibuprofen) 20 (1.0%)</td>
</tr>
<tr>
<td>APC</td>
<td>Prevent colorectal adenomas (3 years)</td>
<td>celecoxib 200 mg bid (n= 685) vs. celecoxib 400 mg bid (n= 671) vs. placebo (n=679)</td>
<td>17 (0.82)</td>
<td>6(0.29)</td>
<td>2.8 (1.1, 7.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 (0.99)</td>
<td></td>
<td>3.4 (1.4, 8.5)</td>
</tr>
<tr>
<td>PreSAP</td>
<td>Prevent colorectal adenomas (3 years)</td>
<td>celecoxib 400 mg qd (n= 933) vs. placebo (n=628)</td>
<td>21 (0.86)</td>
<td>12 (0.72)</td>
<td>1.2 (0.6, 2.4)</td>
</tr>
<tr>
<td>ADAPT</td>
<td>Prevent Alzheimer’s disease (AD) in subjects with family hx of AC (median treatment 14-16 months)</td>
<td>celecoxib 200 mg bid (n= 726) vs. naproxen 220 mg bid (n=719) vs. placebo (n=1083)</td>
<td>(celecoxib) 17</td>
<td>(placebo) 22</td>
<td>1.1 (0.6, 2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(naproxen) 23</td>
<td></td>
<td>1.6 (0.9, 2.8)</td>
</tr>
</tbody>
</table>

*except where otherwise noted as %
Consult: Pharmacodynamic interactions of aspirin with ibuprofen or celecoxib

Center for Drug Evaluation and Research
Multidisciplinary Consult

DATES: Consult Request Date: January 10, 2017
Requested Completion Date: March 6, 2017
Consult Completion Date: July 24, 2017

FROM: Sudharshan Hariharan, Ph.D.
Division of Clinical Pharmacology I

Martin Rose, M.D., J.D., Clinical Team Leader
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Mehul Mehta, Ph.D., Supervisory Pharmacologist,
Division of Clinical Pharmacology I

Norman Stockbridge, M.D., Ph.D., Division Director
Division of Cardiovascular and Renal Products, HFD-110

SUBJECTS: The ibuprofen-aspirin interaction
The celecoxib-aspirin interaction

SPONSOR: Pfizer (Advil® ibuprofen OTC)
G.D. Searle, a Pfizer subsidiary (Celebrex® celecoxib)

NAME OF DRUG: Advil® ibuprofen 200 mg tablets (also higher strengths by prescription)
Celebrex® celecoxib 100 mg capsules

FORMULATION: All relevant NSAID products are IR formulations for oral administration.

RELATED APPLICATIONS: Advil: NDA 01989 and other NDAs
Celebrex: NDA 020998

INDICATIONS: See Appendix I
1. Consult Questions

The following is copied from the consult request. Specific questions are highlighted:

"In 2005, Wyeth submitted three studies looking at the ibuprofen-ASA interaction. The results of the Wyeth studies contributed to the posting of an FDA Science paper about the ibuprofen-ASA drug interaction and the addition of a statement to OTC ibuprofen product labeling suggesting that patients who take ASA should speak to their doctors before taking ibuprofen because it may decrease the efficacy of ASA for cardioprotection. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110510.htm

"Similar changes were NOT made to prescription ibuprofen products at that time because the doses studied were lower than Rx doses. Given the current interpretation of the Bayer study on naproxen-ASA interaction that we would expect the interaction demonstrated in trial 15525 may occur with higher (prescription) doses of naproxen after their discontinuation, but likely at a later time point during washout, we would like to have OCP/DCRP review the ibuprofen-ASA interaction studies for their relevance to higher prescription ibuprofen doses. We request that OCP/DCRP opine on the optimal timing of ibuprofen and ASA ingestion relative to one another in order to maximize the benefit of ASA for cardioprotection.

"Additionally, Pfizer submitted two published celecoxib-ASA interaction studies to support labeling that there is NOT an interaction between celecoxib and ASA. We request OCP/DCRP to review these studies as well to determine whether the submitted data support that conclusion."

The questions regarding ibuprofen and celecoxib will be addressed serially, with separate background discussions and recommendations.

2. Ibuprofen-Aspirin Interaction

2.1 Background

The interaction of aspirin and NSAIDS on the effects of COX-1-mediated formation of thromboxane A2 (TXA2) in platelets was well-described by Dr. Preston Dunnmon of DCRP in his consult regarding the naproxen-aspirin interaction (TSI 490, DARRTS date 9/6/2016):

"Non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase-1 (COX-1) prevent the conversion of arachidonic acid (AA) to thromboxane, thereby blocking thromboxane-induced platelet aggregation. It is by this mechanism that COX-1 inhibiting NSAIDS prevent cardiovascular (CV) events in vulnerable individuals (FDA Science Paper on interaction between low dose aspirin and OTC doses of ibuprofen).

"Aspirin is an irreversible inhibitor of COX-1 as a result of its acetylation of Ser529 (thereby preventing AA from contacting Tyr385). All other NSAID inhibitors of COX-1 are reversible inhibitors of this enzyme. Propionic acid-derived non-aspirin NSAID inhibitors of COX-1, such as ibuprofen and naproxen, are thought to bind reversibly to the same platelet binding site that aspirin acetylates (Ser529). While platelet bound, ibuprofen and naproxen confer an antiplatelet effect. However,
because they are reversibly bound (i.e. disassociate from the platelet as their serum concentration falls), it is possible that they interfere with the permanent antiplatelet effect of aspirin by leaving unacetylated platelets behind as they dissociate from their platelet binding sites.

"This effect has been shown in human ex vivo studies with ibuprofen that demonstrate an ibuprofen-induced attenuation of the expected aspirin-mediated irreversible inhibition of thromboxane B\textsubscript{2} (TXB\textsubscript{2}) production as well as an attenuation of the consequent aspirin-mediated attenuation of platelet aggregation. Accordingly, dosing recommendations to take immediate release aspirin at least 30 minutes before ibuprofen have been made so as to avoid the ibuprofen-aspirin interaction."

Dr. Dunnmon's consult included a review of a 6-arm pharmacodynamic trial conducted by Bayer (Protocol No. 15525) at our request. The trial explored the effects of naproxen, given at various doses and times relative to aspirin dosing, on the effects of daily administration of immediate release (IR) aspirin 81 mg tablets in 10 to 15 evaluable volunteers/arm (see below for description of the treatment arms). In the study, aspirin was given once daily every day from Day 1 through Day 20. Naproxen or no additional treatment was given for 10 days during this period, on days 7 through 16. The primary endpoint was inhibition of ex-vivo generation of thromboxane B\textsubscript{2} (TXB\textsubscript{2}) 24 hours post-dose on Day 16 compared to a baseline measurement. TXB\textsubscript{2} concentration was assessed in blood allowed to clot in an untreated glass tube at 37\degree C. This is a standardized assessment of the activity of COX-1 in the biosynthesis of TXA\textsubscript{2} from arachidonic acid.\textsuperscript{1}

Dr. Dunnmon’s description of dosing in the six arms ("groups") on days 7 through 16, along with his interpretive comments (in italics), are copied below from his consult:

*Group 1 – 10 days of ASA (IR 81 mg) and NAP (220 mg QD) given concomitantly
  o represents the reality that these drugs are frequently taken together*

*Group 2 – 10 days of NAP (220 mg QD) 30 min before ASA
  o functions as positive control for the trial to ensure assay sensitivity if an interaction does indeed exist*

*Group 3 – 10 days of NAP (220 mg QD) administered 8 hours before ASA
  o addresses the question regarding how many hours after an NAP dose that ASA can be taken without loss of platelet inhibition*

*Group 4 – 10 days of ASA alone
  o Functions as negative control for the trial*

*Group 5 – ASA administered 30 min before NAP (220 mg QD)
  o addresses the question regarding how many hours after an NAP dose that ASA can be taken without loss of platelet inhibition, as well as the question as to whether NAP administered after ASA interferes with ASA's antiplatelet effect*

*Group 6 – 10 days of NAP (220 mg bid 12 hours apart) where first dose is 30 minutes before IR ASA 81 mg qd
  o We would anticipate this BID dosing regimen as a worst case scenario for an interaction if one does indeed exist. "*

\textsuperscript{1} TXA\textsubscript{2} has a half-life of about 30 seconds and thus is difficult to quantify accurately. It is rapidly transformed to TXB\textsubscript{2}, either in vivo or ex vivo. The latter substance is inactive, has a reported half-life ranging from 5 to 30 minutes and is much more accurately quantified than the former. A commercially available immunoassay was used to quantify TXB\textsubscript{2} in this study.
Dr. Dunnmon concluded that...“interference by NAP with the antiplatelet effect of low dose ASA was present in all NAP-ASA combination treatment groups, regardless of the timing of the administration of the two drugs, as demonstrated by the lower bound of one-sided 95% CI of the mean of serum TXB2 inhibition [24 hours after the aspirin dose given on Day 16] decreasing to a value of less than 95%....” In addition, treatment with naproxen on Days 7 to 16 was associated in each combination group with impairment of ASA-induced TXB2 inhibition at one or more of the six assessments performed throughout Day 17, the day following the last dose of naproxen. Also, in the case of Group 6, whose members received naproxen 220 mg bid, impairment of ASA-induced TXB2 inhibition was also observed on Day 19, three days after the last dose of naproxen, at each of the six assessments performed from hour 1 to hour 24.

Ibuprofen shares structural and functional characteristics with naproxen. Both drugs are propionic acid derivatives and are relatively non-selective in terms of COX-1 vs. COX-2 EC-50 concentrations. Naproxen has a longer half-life than ibuprofen (12 to 17 hours vs. ~2 hours). Recommended dosing of naproxen tablets OTC is q 8 to 12 hours, and for prescription immediate release tablets, usually bid. For OTC ibuprofen recommended dosing is q 4 to 6 hours and for prescription immediate release tablets, tid or qid for some indications and q 4 to 6 hours for others. Nonetheless, one would expect ibuprofen to have qualitatively similar interactions with aspirin-induced platelet inhibition as naproxen, although one might expect differences in the time course of these interactions due to differences in half-life and dosing intervals.

### 2.2 Ibuprofen-Aspirin Interaction Studies

In 2005, Wyeth submitted to FDA three studies it conducted regarding the ibuprofen-aspirin interaction affecting platelet function. They state that these studies were performed in response to a 2001 publication by Catella-Lawson et. al. This publication and the three studies performed by Wyeth are reviewed below.

#### 2.2.1 Catella-Lawson et. al. 2001 (1)

This publication involved two pharmacodynamic studies performed at the University of Pennsylvania. The research was supported was supported by an NIH grant as well as funding from Bayer Consumer Care.

In the first study, healthy volunteers 18-65 who were within 30% of ideal body weight and who abstained from the use of aspirin or any NSAID for two weeks prior to enrollment were randomized to receive the following medications once daily for six days in each period in a two period crossover study, with a washout period of at least 14 days between periods:

- aspirin 81 mg two hours before ibuprofen 400 mg in the first period, then the same medications in the reverse order in the second period
- aspirin 81 mg two hours before acetaminophen (1000 mg) in the first period, then the same medications in the reverse order in the second period
- aspirin 81 mg two hours before rofecoxib 25 mg (the maximum recommended daily dose in US labeling before the drug was withdrawn from the market) in the first period, and then the same medications in the reverse order in the second period.

In this study, the first medication in the dosing sequence was given at 8 AM on all days in all subjects. Notably, the release characteristics of the aspirin formulation were not described. However, there is a tacit suggestion that it was an IR formulation, because in the second study, the aspirin formulation used was repeatedly described as “enteric-coated.”
The second study was a parallel-group, randomized, open-label, six-day study in subjects with the same characteristics as the first. In this study, one group was given enteric-coated aspirin 81 mg at 8 a.m. and ibuprofen 400 mg at 10 a.m., 3 p.m., and 8 p.m. Thus, there were 12 hours between the evening dose of ibuprofen and the morning dose of aspirin, and then two hours between the aspirin dose and the morning dose of ibuprofen. The other group was given enteric-coated aspirin at 8 a.m., and diclofenac 75 mg at 10 a.m. and 6 p.m. It is not clear whether subjects were confined during either study.

The publication suggests in "Methods" that the first study was planned to include 6 subjects per treatment arm, and the second study was planned to include 5 subjects per treatment arm. However, the number of subjects actually enrolled in either study or included in any analysis is not specified.

In both studies, the inhibition of platelet COX-1 activity was assessed by measurement of serum TXB$_2$ formation in clotted blood and also by platelet aggregation in platelet-rich plasma (PRP) stimulated by arachidonic acid 1.33 µM. These assessments were the primary focus of the two studies. Blood was drawn for assessments of TXB$_2$ and platelet aggregation at multiple time points on the day of dosing in the first study and on Day 6 of dosing in the second study. Also, in the first study only, biosynthesis of prostaglandin I$_2$ (PGI$_2$, also known as prostacyclin) was assessed by measurements of urinary 2,3-dinor-6-keto prostaglandin F$_{1,2}$, and COX-2 activity was assessed through measurement of the formation of lipopolysaccharide-stimulated prostaglandin E$_2$ in whole blood.

**Results – Study 1**

Three subjects who withdrew before receiving study drug were replaced. All subjects who received study drug completed the study. No additional information about subject flow was provided. Also, no information regarding demographic characteristics of the subjects was provided.

The authors stated that they examined the data for period effects and found none. Consequently, data from patients who received a specific regimen in either regimen were pooled for analysis.

Results for inhibition of TXB$_2$ formation and platelet aggregation on day 6 of dosing are shown for the ibuprofen + aspirin and rofecoxib + aspirin pairs are shown in Error! Reference source not found..

For aspirin + ibuprofen, inhibition of TXB$_2$ formation and platelet aggregation was near-complete at all time points assessed when aspirin was given before ibuprofen. However, when ibuprofen was given before aspirin, there was substantial loss of inhibition of both TXB$_2$ formation and platelet aggregation at all assessments later than 2 hours after the first dose of medication. This finding is consistent with a concentration-dependent effect of ibuprofen on COX-1 activity that wanes quickly after hour 2, along with blockade of aspirin-induced acetylation of COX-1 early after dosing with ibuprofen.
Figure 1  Study 1: Inhibition of TXB₂ Formation and Platelet Aggregation on Day 6

A different pattern was observed with rofecoxib + aspirin. Regardless of the order of administration of these drugs, inhibition of TXB₂ formation and platelet aggregation were near complete at all time points. This is consistent with the low affinity of rofecoxib for COX-1.

Data for aspirin + acetaminophen were presented in the publication in text: Acetaminophen had no apparent effect on aspirin-induced effects on TXB₂ formation or platelet aggregation regardless of the order of administration, consistent with the limited COX-1 inhibiting effect of acetaminophen.

Assessment of COX-2 activity through inhibition of formation of prostaglandin E₂ showed greater and more persistent inhibition of enzymatic activity with rofecoxib than with ibuprofen or acetaminophen, as expected. Likewise, assessment of PGI₂ synthesis by measurement of urinary 2,3-dinor-6-keto prostaglandin F₁α also showed a greater inhibitory effect of rofecoxib than the other two tested.
drugs, consistent with the fact that in healthy adults, most PGI$_2$ is produced in cells where COX-2 is the major cyclooxygenase isoform.

Results – Study 2

One subject with a viral illness who was treated with non-study NSAIDs was replaced. No additional information about subject flow or characteristics was provided.

In this study, where ibuprofen was given 3 times daily, and the aspirin formulation was enteric coated, there was substantial loss of aspirin-induced inhibition of TXB$_2$ formation day 6 at hours 12 and 24, and a substantial loss of inhibition of platelet aggregation at hours 2, 12 and 24. The first dose of ibuprofen was given two hours after the daily aspirin dose. This suggests that with thrice daily dosing of ibuprofen, the aspirin-blocking effect of ibuprofen may persist overnight, even though ibuprofen's direct effects on platelet inhibition are greatly diminished from its peak effect, and/or the two hour delay between the 8 AM aspirin dose and the 10 AM ibuprofen dose was not long enough for a sufficient quantity of aspirin to be absorbed and to affect platelets before being blocked by ibuprofen. The study does not provide information that could inform a decision regarding when ibuprofen could be given so that it would not interfere with the platelet-inhibiting effects of enteric-coated aspirin.

On the other hand, twice daily controlled release diclofenac was associated with substantially less loss of aspirin-induced inhibition of TXB$_2$ formation and platelet aggregation than was ibuprofen, consistent with the reduced affinity of diclofenac for COX-1 and its comparatively short duration of action. The PK characteristics of the diclofenac formulation were not described.

Figure 2 Study 2: Inhibition of TXB$_2$ Formation and Platelet Aggregation on Day 6

Assessment

This publication indicates that when a single dose of immediate-release aspirin 81 mg was given two hours before ibuprofen 400 mg, there was near-complete inhibition of TXB$_2$ production for 24 hours, meaning that ibuprofen did not interfere with the effect of aspirin. However, if an enteric-coated formulation of aspirin had been given instead of immediate release aspirin, it is possible that...
ibuprofen might have interfered with the effect of aspirin on platelets if the ibuprofen was given only two hours after aspirin.

When single doses of the same drugs were given in the reverse order, TXB$_2$ inhibition was near-complete only at 2 hours. Over the next 22 hours, the level of inhibition dropped progressively, reaching ~50% at hour 24. This is consistent with substantial interference with aspirin-induced platelet COX-1 inhibition by ibuprofen, along with a direct but short-lived inhibitory effect of ibuprofen on COX-1. However, for much of the day, COX-1 inhibition would be low enough so that patients with coronary artery disease would be at increased risk for thrombotic events compared to those who took aspirin alone.

On the other hand, administration of rofecoxib before or after a single dose of aspirin did not affect aspirin-induced inhibition of TXB$_2$ generation.

In the 6 day study included in the Catella publication, two potential mechanisms might have contributed to the reduced inhibition TXB$_2$ generation and platelet aggregation that was observed in patients who received tid ibuprofen 400 mg (given at 10AM, 2 PM and 8 PM) after an 8 AM enteric-coated aspirin dose compared to those received placebo for ibuprofen: (1) the possibility that accumulation of ibuprofen over 6 days resulted in a sufficient blood concentration of the drug remaining at 8 AM to interfere with the effect of the 8 AM aspirin dose, and/or (2) because of the use of slowly absorbed enteric-coated aspirin in this study, the two hour window between the 8 AM dose of aspirin and the 10 AM dose of ibuprofen was too short to allow a sufficient number of platelets to be acetylated by aspirin before ibuprofen absorbed from the 10 AM dose began to interfere with platelet acetylation. Without additional information, one cannot determine the extent to which either of these mechanisms contributed to the observed reduction in platelet inhibition. One cannot use the results of this study to define the optimal way to give ibuprofen chronically to a patient taking aspirin for secondary prevention of CV disease.

### 2.2.2 Wyeth Study AA-02-21: Antiplatelet Effects of Aspirin followed by Ibuprofen

This is the first of three studies performed and submitted by Wyeth. They will be presented in ascending order of protocol number. The studies assessed the effects of ibuprofen on aspirin-induced platelet inhibition in three scenarios: aspirin given before ibuprofen, each given once daily for 6 days (Study 02-21); ibuprofen given before aspirin, each given once daily for 6 days (Study 02-22); and aspirin given once daily with ibuprofen given tid for 10 days (Study 04-24). An integrated assessment of the studies follows the description of the third study.

The objective of study 02-21 was to determine whether a single daily dose of ibuprofen 400 mg interfered with the antiplatelet effects of aspirin (81-mg, immediate release, non-enteric coated) when given immediately following, or up to 2 hours after aspirin administration.

This was a two-way crossover study in 31 healthy volunteers performed at a single center, the Dallas VA Medical Center. The PI was Byron Cryer, MD.

Subjects were volunteers aged 18-65 years who were within ± 30% of ideal weight, in good health, and who refrained from ingesting any medication other than oral contraceptives, hormone replacement, or acetaminophen for 14 days prior to enrollment and from alcohol for 12 hours prior to each blood draw.

Subjects were randomized to receive two of the four following treatment regimens serially. The likelihood of a subject receiving any of the 12 possible sequences of study regimens was similar.

- Regimen 1: Aspirin 81 mg immediate release each morning followed immediately by 2 Advil (ibuprofen) tablets 200 mg (total dose 400 mg) once daily for 6 days
• Regimen 2: Aspirin 81 mg immediate release each morning followed 15 minutes later by 2 Advil tablets 200 mg once daily for 6 days
• Regimen 3: Aspirin 81 mg immediate release each morning followed 30 minutes later by 2 Advil tablets 200 mg once daily for 6 days
• Regimen 4: Aspirin 81 mg immediate release each morning followed 2 hours later by 2 Advil tablets 200 mg once daily for 6 days (intended as a negative control)

Aspirin given in this study was provided by Bayer as 81 mg immediate release, chewable tablets. Such tablets are commercially available in the US, although it is not clear whether the tablets now available for purchase are the same as those used in the study.

On Day 1, after blood draws for baseline TXB_2 testing and platelet aggregation studies, patients had breakfast and then one hour later received aspirin and then ibuprofen consistent with their treatment assignment, all in the study unit. They went home and then returned to the unit on the morning of Days 2 - 6 for a similar routine (except for the blood draws).

On Day 7, they returned to the unit, had breakfast, and then blood was drawn for TXB_2 and platelet aggregation studies 24 hours after the last dose of aspirin. They then entered a 14 day washout period, returned to the unit, and repeated the previous procedures for Days 1-7 with a different randomized treatment.

The primary outcome parameter was percent inhibition of TXB_2 formation in whole blood drawn 24 hours after the Day 6 aspirin dose, and incubated for one hour in a glass tube in a 37°C water bath. The secondary outcome parameter was percent inhibition of platelet aggregation (in PRP from blood drawn at the same time as blood for the primary outcome, stimulated by arachidonic acid at a final concentration of 500 mcg/mL).

Results

Thirty one subjects were enrolled, and all completed two periods of treatment as planned. Results for the primary and secondary outcome parameters are shown in

Table 1, Figure 3, and Figure 4.
Table 1 Study AA-02-021: Primary and Secondary Outcome Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment regimen: aspirin 81 mg, followed by ibuprofen 400 mg, given --- #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediately</td>
</tr>
<tr>
<td><strong>TXB₂ Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>15</td>
</tr>
<tr>
<td>Median (25th, 75th pctl)</td>
<td>72.7 (45.7, 61)</td>
</tr>
<tr>
<td>Mean (s.d.)</td>
<td>71.1 (27.8)</td>
</tr>
<tr>
<td>n(%) with &gt; 90% inhibition</td>
<td>6 (40%)</td>
</tr>
</tbody>
</table>

**Platelet Aggregation Inhibition**

|                                  |             |                 |                 |                  |
| n                                | 16          | 15              | 15              | 15               |
| Median (25th, 75th pctl)         | 46.9 (0.0, 94.6) | 94.5 (84.2, 97.2) | 95.9 (91.0, 97.1) | 94.1 (86.5, 95.7) |
| Mean (s.d.)                      | 47.4 (48.2) | 82.6 (29.6)     | 93.5 (7.0)      | 90.5 (7.1)       |
| n(%) with > 90% inhibition       | 8 (50%)     | 11 (73%)        | 14 (93%)        | 9 (60%)          |

* The primary and secondary outcomes were TXB₂ inhibition and platelet aggregation inhibition (agonized by arachidonic acid), respectively. Each outcome was assessed 24 hours after the aspirin dose given on Day 6 and compared to baseline (pre-treatment) results for the relevant outcome to derive % inhibition. # Data column headers describe the timing of ibuprofen administration relative to aspirin administration.

Figure 3 Study AA-02021: Primary Outcome Results – Inhibition of TXB₂ Formation
The results for the primary outcome of inhibition of TXB₂ formation 24 hours after the Day 6 aspirin dose are consistent with the results of the Catella-Lawton paper and the accepted mechanism of aspirin’s effect on platelets and the aspirin-ibuprofen interaction. Absorption of immediate release aspirin from the GI tract is nearly complete in one hour.(2) Platelet inhibition is rapid after absorption and lasts for the life of the platelet. Thus, when ibuprofen is given two hours after aspirin, one would expect absorption of aspirin to be complete at the time of dosing with ibuprofen, resulting in an observation of the full effect of aspirin on platelets the next day—i.e., near-complete inhibition of TXB₂ formation. That is what was observed. As the time gap from aspirin dosing to ibuprofen dosing was narrowed from two hours to 30 minutes to 15 minutes to essentially contemporaneous dosing, TXB₂ inhibition was progressively reduced, reaching a nadir of about 70% for median inhibition when ibuprofen was given immediately after aspirin. Results for the secondary endpoint of platelet aggregation show a pattern of ~95% median inhibition for the groups where ibuprofen was given 15 minutes or more after aspirin. Only the group where it was given immediately after aspirin had substantially reduced median inhibition (47%).

2.2.3 Study AA-02-22: The Antiplatelet Effects of Aspirin Preceded by Ibuprofen

This was an outpatient, single-center, randomized, two-way crossover study in healthy adult subjects. It was performed at the same site and by the same PI as the previous study.

The primary objective was to determine when immediate-release aspirin 81 mg can be given following dosing with ibuprofen 400 mg without interfering with platelet aggregation. This was to be determined on the basis of the TXB₂ inhibition 24 hours after the last dose of aspirin (taken on Day 6) when ibuprofen was taken 8 hours prior to aspirin. The hypothesis tested was that there would be at least 90% inhibition at this time.

Subjects were adult volunteers similar to those in the previously described Wyeth 02-21 study, except that there was one additional and quite valuable inclusion requirement: they had to have ≥90% inhibition of TXB₂ formation compared to baseline after a regimen of 81 mg of study aspirin daily x 3 days given during the screening period.

Consult: Pharmacodynamic interactions of aspirin with ibuprofen or celecoxib
Those who met the inclusion criteria were randomized after a 21 day aspirin washout to receive two of the five treatment regimens in a random-sequence, 2-period cross-over design, with a 21 day washout between the two randomized treatment periods. A total of 39 patients were to be randomized. The regimens were:

- Regimen 1: aspirin 81 mg tablet each morning for six days
- Regimen 2: ibuprofen 2 x 200 mg tablets (total dose 400 mg) each morning, followed by aspirin 81 mg tablet two hours later for six days.
- Regimen 3: ibuprofen 2 x 200 mg tablets each morning, followed by aspirin 81 mg tablet four hours later for six days.
- Regimen 4: ibuprofen 2 x 200 mg tablets each morning, followed by aspirin 81 mg tablet six hours later for six days
- Regimen 5: ibuprofen 2 x 200 mg tablets each morning, followed by aspirin 81 mg tablet eight hours later for six days.

The aspirin used in the study was commercial Bayer 81 mg Children’s Chewable Aspirin, which is an immediate release product. The ibuprofen was commercial Advil 200 mg tablets.

Notably, no patient received ibuprofen tid or qid, as it is often given when taken chronically. Multiple daily dosing would be associated with a greater likelihood of accumulation, which could affect the duration of ibuprofen blockade of aspirin-induced platelet acetylation and its effects on platelet function.

Blood samples for PD studies were taken 3 times during the treatment period:

- Day 1, prior to IBU dosing (prior to aspirin dosing for regimen 1);
- Day 7, 24 hr after Day 6 aspirin dosing, and;
- Day 7, 24 hr after Day 6 ibuprofen dosing (except for regimen 1)

The PD studies were assays of TXB₂ and platelet aggregation using an arachidonic acid agonist (final concentration 500 mcg/mL, as in the study 02-21). Separate venipunctures were performed to obtain the blood for each of the two tests at each of the scheduled times.

This was an outpatient study. However, subjects were given a pager and were paged 30 minutes prior to each scheduled dose of study medication. They were to come to the clinic and take each dose of study medication under observation. This procedure was followed during the aspirin screening phase as well as during randomized treatment.

**Results**

Forty-nine subjects entered the screening phase; 5 subjects (10.2% had < 90% inhibition of TXB₂ after 3 days of aspirin treatment and were considered screen failures. Nine other subjects withdrew prior to entering period 1 due to withdrawal of consent or scheduling issues. The remaining 35 subjects, plus 2 subjects who were among the 5 who failed to sufficiently respond to aspirin during the screening period, entered the study and completed both study periods. The two who did not respond to aspirin but were mistakenly treated are excluded from the per-protocol analyses below because they were considered to be not evaluable. They were included in ITT analyses (data not shown). Our view is that excluding the two aspirin non-responders from the per-protocol analyses of TXB₂ and platelet aggregation was appropriate.

Results of platelet function studies performed on blood drawn 24 hours after Day 6 aspirin dosing are shown in **Table 2** and **Figure 5**, while results of platelet function studies performed 24 hours after Day 6 ibuprofen dosing are shown in **Table 3** and **Figure 6**. The two tables show similar patterns of data, as do the two figures, but the aspirin only period is not represented in Table 3 and **Table 2**.
Figure 6. Also, Figure 7 is a plot of the individual data points that are summarized in Figure 5. As in previous studies, near-complete (~95%) inhibition of TXB$_2$ generation with little variability between patients was observed with aspirin alone. With aspirin alone, mean platelet aggregation was 91%, with an SD less than 2%. When ibuprofen was given 2 hours before aspirin, inhibition of TXB$_2$ generation was ~50%, and mean inhibition of platelet aggregation was 17%, with an SD of 7.5%. As the time between ibuprofen administration and aspirin administration was lengthened progressively to 4, 6, and 8 hours, inhibition of TXB$_2$ generation and platelet aggregation increased, but never reached the high mean levels and low variability observed with aspirin alone. Even when ibuprofen was given 8 hours prior to aspirin, there was interference of aspirin-induced inhibition of TXB$_2$ generation and platelet aggregation 24 hours after aspirin or ibuprofen dosing. The interference was of a magnitude that would raise concern about increased risk of thrombotic CV events. Thus in this study, administration of once daily doses of ibuprofen either 2, 4, 6 or 8 hours prior to aspirin for 6 days resulted in interference with the therapeutic effect of aspirin on platelets that we think could be clinically significant in patients taking aspirin for prevention of CV events.

Table 2  Study 02-22: Percent Inhibition of Outcome Parameters 24 hours after Day 6 Aspirin Dosing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASA only (Regimen 1)</td>
</tr>
<tr>
<td><strong>TXB$_2$ Inhibition (%)</strong></td>
<td>n</td>
</tr>
<tr>
<td>TXB$_2$ Inhibition (%)*</td>
<td>15</td>
</tr>
<tr>
<td><strong>Platelet Aggregation Inhibition (%)</strong></td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviations: IBU=ibuprofen; ASA=aspirin 81 mg

* The primary and secondary outcomes were TXB$_2$ inhibition and platelet aggregation inhibition (agonized by arachidonic acid), respectively. Each outcome was assessed 24 hours after the aspirin dose given on Day 6 and compared to baseline (pre-treatment) results for the relevant outcome to derive % inhibition.
### Table 3  Study 02-22: Percent Inhibition of Outcome Parameters 24 hours after Day 6

**Ibuprofen Dosing**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IBU 2 hours Before ASA (Regimen 2)</th>
<th>IBU 4 hours Before ASA (Regimen 3)</th>
<th>IBU 6 hours Before ASA (Regimen 4)</th>
<th>IBU 8 hours Before ASA (Regimen 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TXB₂ Inhibition (%)*</td>
<td>n 13</td>
<td>14</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Median (25th, 75th pctle)</td>
<td>(39.6, 56.4)</td>
<td>(50.4, 85.7)</td>
<td>(82.9, 90.4)</td>
</tr>
<tr>
<td></td>
<td>Mean (s.d.)</td>
<td>50.18 (5.5)</td>
<td>62.64 (8.3)</td>
<td>81.43 (5.0)</td>
</tr>
<tr>
<td>Platelet Aggregation Inhibition (%)*</td>
<td>n 14</td>
<td>13</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Median (25th, 75th pctle)</td>
<td>0.35</td>
<td>0.0</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>Mean (s.d.)</td>
<td>7.64 (3.2)</td>
<td>3.04 (1.6)</td>
<td>29.21 (11.2)</td>
</tr>
</tbody>
</table>

Note: Data for Regimen 1 (aspirin without ibuprofen) are omitted

### Figure 5  Study AA-02-22: Percent Inhibition of Outcome Parameters 24 Hours after Day 6

**Aspirin Dosing**

Consult: Pharmacodynamic interactions of aspirin with ibuprofen or celecoxib
2.2.4 Study AA-04-24: The Effects of Repetitive Dosing of Ibuprofen on the Antiplatelet Activity of Aspirin.

The objective of this study was to determine whether a TID dosing regimen of IBU 400 mg taken for 1, 3, 7 or 10 consecutive days interfered with antiplatelet activity in subjects who had been pretreated with and continued on a regimen of once daily immediate release, chewable ASA 81 mg.
This was randomized, double-blind, placebo controlled parallel arm, outpatient study in 51 healthy volunteers. It was performed at the same single study site as the two previously described studies, and had the same PI.

Study subjects were similar to those in study 02-22. Like those in 02-22, they were screened for aspirin responsiveness, using the same criteria as in the previous study, i.e., a requirement of \( \text{TXB}_2 \) inhibition of at least 90\% after dosing with 81 mg immediate release aspirin daily. See below for additional details.

Fifty-one subjects entered the treatment phase of the study. All subjects received open label aspirin 81 mg once daily at 8 AM for 18 days (Study Days 1 to 18). Starting on study day 9, in addition to the aspirin at 8 AM they also received randomized study medication three times daily (ibuprofen 400 mg or placebo) until Day 18, a total of 10 days. Randomized treatments were as follows:

- **Treatment A:** Two ibuprofen 200 mg liquigels (totaling 400 mg) TID at 1, 7, and 13 hours post ASA dosing (i.e., approximately at 9 AM [morning dose], 3PM [midday dose], and 9 PM [evening dose]).
- **Treatment B:** Two placebo liquigels on the same schedule as Treatment A.

Study aspirin was the same as in the study 02-22 -- Bayer 81 mg Children's Aspirin Chewable Tablet, an immediate release product sold in the US. Ibuprofen study drug was identified as "IBU Liquigel" (200 mg/liquigel). It is not clear if this was an investigational or commercial product.\(^2\)

The study plan was as follows:

At the screening visit, subjects had a history, physical exam and routine laboratory testing, as well as blood draws for baseline determinations of \( \text{TXB}_2 \) and platelet aggregation. They returned within 14 days for Visit 1 (Study Day 1). Those who were eligible for enrollment received a bottle of aspirin tablets, and took their first dose in the clinic. They were given pager and a drug administration diary. They were told take 1 aspirin tablet daily at the same time each day, and record the date and time of ingestion in the diary. They were paged each day 30 minutes before the planned time for taking study drug, which was taken outside the clinic. They were also paged to remind them of study visits.

They returned to the site on Day 9 at 7:30 AM. At that time they were assessed for continuation into the randomized phase of the study. Blood was drawn and immediately assessed for \( \text{TXB}_2 \) formation while patients waited. Only those with \( \text{TXB}_2 \) inhibition of at least 90\% progressed to the randomized phase. They were randomized and given a bottle of blinded study drug (ibuprofen or placebo, see above) and dosing instructions consistent with the descriptions of Treatment A and B above. They took their first dose of randomized study medication and then went home with their blinded study medication, their open label aspirin, and their pager. They returned to the clinic each day to take their first daily dose of randomized study medication daily until day 18, the last of treatment with open label aspirin and double-blind study drug.

They returned to the clinic on Day 19 for their final blood draws for \( \text{TXB}_2 \) and platelet aggregation inhibition. \( \text{TXB}_2 \) inhibition was also assessed on Days 1, 9, 10, 12 and 16.

The outcome parameters were:

- Percent inhibition of \( \text{TXB}_2 \) on days 9, 10, 12, 16 and 19.

\(^2\) This study was conducted from February to May in 2004. Advil Liquigels 200 mg entered the US OTC market in 2000.
The percentage of subjects with at least 90% inhibition of TXB\(_2\) on days 9, 10, 12, 16, and 19. Note that subjects were started on ibuprofen or placebo on Day 9.

The treatment arms were compared with respect to TXB\(_2\) inhibition by ANOVA with treatment group as the sole factor. In addition,

"In order to obtain data that approximates a normal distribution, the proportions of TXB\(_2\) inhibition (from Day 9 to Day 19 sample values) were transformed via the angular transformation for the purpose of statistical analysis of serum TXB\(_2\) percentage inhibition. The within and between-treatment 95% (one-sided) confidence limits for each treatment regimen were computed using the observed means and the standard errors within the treatment regimen (on the transformed scale). The within treatment confidence limits were back transformed to the original scale in order to compare with the 90% cut-off point."

**Results**

All 51 subjects who entered the aspirin screening period completed that period and were randomized. However, 2 subjects did not meet the aspirin response criteria and were not included in the per-protocol or ITT analyses (total N=49, with 25 and 24 in the placebo and ibuprofen arms, respectively). Two subjects had "significant" protocol violations regarding dosing of study medication and were not included in the per-protocol analyses, (total N=47, with 24 and 23 in the placebo and ibuprofen arms, respectively).

Demographic information for the per-protocol population in the treatment arms is shown in **Table 4**. The two arms were similar for all reported characteristics.

<p>| Table 4 Study 04-24: Demographic Information, Per Protocol Population |
|---|---|---|
| | Placebo N=24 n (%) | Ibuprofen 400 mg N=23 n (%) |
| <strong>GENDER</strong> | | |
| MALE | 13 (54.2%) | 12 (52.2%) |
| FEMALE | 11 (45.8%) | 11 (47.8%) |
| <strong>RACE</strong> | | |
| CAUCASIAN | 10 (41.7%) | 13 (56.5%) |
| BLACK | 11 (45.8%) | 7 (30.4%) |
| ASIAN | 1 (4.2%) | 1 (4.3%) |
| HISPANIC* | 1 (4.2%) | 2 (8.7%) |
| OTHER | 1 (4.2%) | 0 |
| <strong>AGE (YEARS)</strong> | | |
| MEAN | 38.0 | 38.9 |
| STD | 10.2 | 9.6 |</p>
<table>
<thead>
<tr>
<th></th>
<th>Placebo N=24 n (%)</th>
<th>Ibuprofen 400 mg N=23 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEDIAN</strong></td>
<td>38.0</td>
<td>38.0</td>
</tr>
<tr>
<td><strong>RANGE</strong></td>
<td>(19.0, 54.0)</td>
<td>(23.0, 53.0)</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td><strong>WEIGHT (POUNDS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>173.3</td>
<td>173.0</td>
</tr>
<tr>
<td><strong>STD</strong></td>
<td>24.2</td>
<td>29.7</td>
</tr>
<tr>
<td><strong>MEDIAN</strong></td>
<td>172.5</td>
<td>179.0</td>
</tr>
<tr>
<td><strong>RANGE</strong></td>
<td>(128.0, 216.0)</td>
<td>(128.0, 221.0)</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td><strong>HEIGHT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>68.3</td>
<td>69.4</td>
</tr>
<tr>
<td><strong>STD</strong></td>
<td>3.3</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>MEDIAN</strong></td>
<td>68.0</td>
<td>71.0</td>
</tr>
<tr>
<td><strong>RANGE</strong></td>
<td>(60.0, 73.0)</td>
<td>(61.0, 76.0)</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td><strong>FRAME</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SMALL</strong></td>
<td>2 (8.3%)</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td><strong>MEDIUM</strong></td>
<td>18 (75.0%)</td>
<td>12 (52.2%)</td>
</tr>
<tr>
<td><strong>LARGE</strong></td>
<td>4 (16.7%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td><strong>ELBOW BREADTH (INCHES)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>STD</strong></td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>MEDIAN</strong></td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>RANGE</strong></td>
<td>(2.3, 3.1)</td>
<td>(2.1, 3.1)</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>24</td>
<td>23</td>
</tr>
</tbody>
</table>

“Hispanic” is used here as a racial classification, not an ethnicity.
Results for TXB₂ inhibition on days 9 (before the start of blinded ibuprofen/placebo treatment), 10, 12, 16, and 19 (after 1, 3, 7, and 10 days of blinded treatment, respectively), are shown in Table 5 and Figure 8.

Although the differences between the treatment arms are small, there is a statistically significant difference in TXB₂ inhibition between the study arms on Days 16 and 19. In addition, variability of TXB₂ inhibition (the SD of the mean) is higher in the ibuprofen arm than in placebo arm of Days 16 and 19, and the lower end of the range of TXB₂ inhibition is somewhat lower in the ibuprofen arm (Day 19 only). The range of values for TXB₂ inhibition on day 19 in the ibuprofen arm was as low as 90% -- less than the lower limit of 95% inhibition associated with clinically effective suppression of platelet activity (see discussion below). Thus, there were detectable and possibly medically important effects of residual ibuprofen blood levels on aspirin-induced acetylation of COX-1 in some patients after a week of tid dosing of ibuprofen.

Notably, the morning aspirin dose was taken 11 hours (about 5 to 7 ibuprofen half-lives) after the previous dose of ibuprofen. One would expect ibuprofen blood concentration to have been quite low at the time of aspirin ingestion. Thus, aspirin could access the acetylation site of COX-1 in many platelets. If on the other hand, the last dose of ibuprofen had been taken at 11 PM, which is bedtime for many adults, and the AM aspirin dose was taken at 7 AM, there would be only 8 hours in between the doses. One might less aspirin absorption and less platelet acetylation in that case, thereby reducing the level of platelet inhibition early the following morning and increasing thrombotic risk. In fact, in the previously described study 02-22, once-daily ibuprofen given 8 hours before aspirin was shown to diminish the anti-platelet activity of aspirin (Table 2 and accompanying text).

Table 5  Study 04-24: Percent Inhibition of TXB₂ (Relative to Day 1) during the 10 Days of Study Medication Treatment after 8 Days of ASA Run-in Dosing

<table>
<thead>
<tr>
<th>TXB₂</th>
<th>Study Day (Days on Blinded Study Medication)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 9 (0 Days)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>24</td>
</tr>
<tr>
<td>Mean</td>
<td>98.72</td>
</tr>
<tr>
<td>SD</td>
<td>1.06</td>
</tr>
<tr>
<td>Median</td>
<td>98.75</td>
</tr>
<tr>
<td>Range</td>
<td>(94.90, 100.0)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>23</td>
</tr>
<tr>
<td>Mean</td>
<td>98.85</td>
</tr>
<tr>
<td>SD</td>
<td>0.64</td>
</tr>
<tr>
<td>Median</td>
<td>98.90</td>
</tr>
<tr>
<td>Range</td>
<td>(97.40, 99.80)</td>
</tr>
</tbody>
</table>

Blood was drawn for assessments of TXB₂ 24 hours after the previous dose of aspirin.
Source: Study A=04-24 CSR, Table 5.

Consult: Pharmacodynamic interactions of aspirin with ibuprofen or celecoxib
Blood was drawn for assessments of TXB₂ 24 hours after the previous dose of aspirin. Source: Study A=04-24 CSR, Figure 1.

In addition, the immediate release aspirin product was given one hour before the first daily dose of ibuprofen, giving it time to be absorbed before the ibuprofen concentration was adequate to block aspirin-induced acetylation of COX-1. However, we believe that most low-dose aspirin sold in the US is enteric coated. If such aspirin had been used in this study, it is likely that acetylation of COX-1 would have been substantially less complete than with use of immediate release aspirin. This would have resulted in a substantially lower degree of TXB₂ inhibition at the time of aspirin dosing on each day, including Day 19.

It is notable that when interpreting the results of TXB₂ inhibition assays, Wyeth emphasizes the 95% CI of the group mean level. They claim that that if the lower end of the CI is not less than 90% in the group receiving ibuprofen and aspirin and aspirin, then one can assume that there was no meaningful interaction between the two drugs affecting aspirin-induced inhibition of COX-1 activity and synthesis of TXA₂. However, as Dr. Dunnmon stated in his previously-cited consult regarding the naproxen-aspirin interaction, we favor use of a more stringent limit: the lower end of the 95% CI of TXB₂ inhibition should be no less than 95% to conclude that the antiplatelet of aspirin is not meaningfully affected by a drug interaction. This conclusion is based on work by Reilly and FitzGerald showing that overall biosynthesis of thromboxane (based on urinary excretion of a TXB₂ metabolite) remains substantial unless ex vivo TXB₂ generation is inhibited by at least 95%. (3). Earlier work by Di Minno et. al. is supportive. (4)³ These data suggest that inhibition of TXB₂ generation in clotted whole needs to be near complete (i.e., 95% or more) before we can assume that the ability of platelets to aggregate and promote thrombosis has been substantially reduced.

³ This group used light transmission aggregometry to assess platelet function. A sample of fresh platelet-rich plasma (PRP) was set at 10% transmission, and sample of platelet-free plasma (PFP) was set as 90%. As platelets aggregate, light transmission increases from the PRP standard towards PFP standard. This group showed in in vitro experiments that when aspirin-treated platelets were mixed with progressively increasing numbers of aspirin-free platelets, a mixture of two endogenous agonists (arachidonic acid and collagen) could produce at least 50% light transmission when aspirin-free platelets made up as little as 2.5% of the total platelet number (compared to ~ 5%-10% transmission with no aspirin-free platelets). When there were 10% aspirin-free platelets, light transmission was ~80%.
Assessment

Even with the somewhat relaxed standard of the 90% CI of mean inhibition, the data suggest that some subjects might have an insufficient degree of COX-1 inhibition at trough levels of ibuprofen in the morning, 11 hours after their last dose of ibuprofen, with the treatment regimens of ibuprofen and aspirin used in this study. Also, we think that an 11 hour difference between the last daily dose of ibuprofen given tid and the morning dose of aspirin is atypical. Even if this regimen were implemented, it might not provide adequate pain relief throughout the day. Even more concerning is the fact that immediate release chewable aspirin was used in this study. There is a reasonable likelihood that results would have been worse in terms of TXB₂ inhibition if an enteric-coated aspirin had been used. Our view is that the results of this study cannot be extrapolated to the use of enteric-coated aspirin, which we think is the dominant form of low-dose aspirin used in the US.

2.2.5 Overall assessment

The 4 studies submitted by Wyeth suggest that ibuprofen has a substantial, concentration-dependent inhibitory effect on COX-1 and can reduce TXB₂ formation in clotted blood substantially. However, ibuprofen inhibits aspirin-induced acetylation of platelets, so that unless the time of dosing is exquisitely controlled, and in some patients, even when it is exquisitely controlled, patients taking tid ibuprofen and once daily low dose aspirin to prevent CV events may have insufficient platelet inhibition to prevent such events at trough levels of ibuprofen. In addition, the test of the interaction between multiday treatment with tid ibuprofen and once daily aspirin was performed with an immediate release chewable aspirin formulation. These results cannot be extrapolated to the use of enteric coated aspirin, which we think is the dominant form of low-dose aspirin in the US. If enteric-coated aspirin had been used in the 04-24 study instead of immediate release aspirin, we think that the degree of inhibition of platelet function would have reduced, and an ibuprofen-aspirin interaction would have been demonstrated.

3. Celecoxib-Aspirin Interaction Studies

Highly selective COX-2 inhibitors would not be expected to have substantial binding to COX-1 and thus might not block acetylation of platelet COX-1 by aspirin. Notably, the Catella-Lawson paper discussed above included a rofecoxib arm, and found no effect of rofecoxib pretreatment for 5 days at the recommended dose on aspirin-induced inhibition of TXB₂ production in clotted blood or platelet aggregation (see Figure 1 and associated discussion). However, rofecoxib is more selective for COX-2 than celecoxib. Nonetheless, celecoxib is 350 times more selective for COX-2 than COX-1, with an IC₅₀ for the recombinant human enzymes of 0.04 μM and 15 μM, respectively (5), suggesting that interaction with aspirin’s effects on COX-1 might be minimal at concentrations that provide substantial inhibition of COX-2.

We were provided with the results of two studies that examined the effects of celecoxib on platelet function and one study regarding its interaction with aspirin.

3.1 Simon et. al. (6)

This study is described only in a published report. It was a 2-period, open-label crossover study in six healthy male volunteers who had not taken any medications or used tobacco for at least two weeks prior to dosing. Subjects were treated with celecoxib 400 mg twice daily for 5 days(2 X the highest recommended dose for administration for more than one day) and then given 400 mg once on the again on the morning of Day 6. Blood was drawn for studies of TXB₂ and platelet aggregation inhibition. After a 14 day washout, subjects ingested a single dose of aspirin 650 mg on study Day 20 and the platelet studies were repeated.
Results

No information on patient flow or baseline characteristics was provided.

The trial shows no effect of high-dose celecoxib on platelet aggregation or thromboxane generation, although the small N might have obscured a small effect. There were no significant differences between the baseline and any of the post celecoxib treatment aggregation values on day 6, while aspirin given on day 20 produced the expected inhibition of platelet aggregation (Figure 9). Pre- and post- celecoxib treatment TXB\textsubscript{2} levels were not significantly different (mean of 11 ng/mL at baseline and 15, 11, and 8 ng/mL at 2, 4 and 12 hours after the celecoxib dose). During the aspirin phase, the baseline level was 9 ng/mL and was undetectable (<0.1 ng/mL) 2 and 4 hours post dose (the 12 hour post-dose value was not described).

Note that this is not a celecoxib-aspirin interaction study because aspirin was administered after a 14 day washout following celecoxib administration. While this study, like the previously discussed rofecoxib study, suggests that use of celecoxib does not impair platelet aggregation, there is no useful information about the effects of celecoxib exposure on aspirin-induced platelet inhibition.

Figure 9 Simon et. al. Collagen-Induced Platelet Aggregation after Celecoxib and Aspirin

3.2 G.D. Searle Study N49-01-06-150

This study is entitled, "A Phase I Double-Blind, Placebo-Controlled Study Designed to Evaluate the Effect of Celecoxib on the Anti-Platelet Activity OF Low-Dose Aspirin in Healthy Subjects" (Report date, 9 April 2001). It was performed by the sponsor of celecoxib at a single US center (Clinical Research Center, New Orleans, LA, Ramon Vargas, PI) under GCP. The study was conducted from March 20 to May 26, 2000. A PDF copy of the report was provided to us by Dr. Racoosin. It was a true celecoxib-aspirin interaction study.

Design: As noted in the protocol title, this was an RCT in confined healthy volunteers with a parallel design. Subjects were screened (including pregnancy testing for women) and randomized to
treatment with celecoxib 200 mg BID or placebo; the plan was to have 8 completers per arm. Subjects were confined at the study center on Day 0 for at least 12 hours before the first dose of study drug on Day 1. Study drug was given on Days 1 to 4 at 8 AM and 8 PM. On the morning of Day 5 at 8 AM, subjects received a single 325 mg dose of aspirin in addition to their last dose of study drug. The aspirin was stated to be “Bayer Aspirin or equivalent.” This was likely to be an immediate release tablet.

Blood samples to measure TxB2 as well as platelet counts and platelet aggregation response to ADP collagen, and arachidonic acid were collected on Day 1 before dosing for the Baseline measurement and on Day 5 before dosing and at 2 and 8 hours after dosing. No concurrent medications other than oral contraceptives were allowed.

Alcohol, caffeine and grapefruit juice were not permitted, beginning 48 hours before the start of the study and continuing through the completion of the study. Water was permitted without restriction.

**Subjects:** Subjects were non-smoking volunteers of either gender age 18 to 55 years. No use of prescription or OTC drugs was allowed in the two weeks prior to enrollment; however, NSAIDS were not allowed for four weeks prior to enrollment. Subjects had to be in good health as determined by a detailed medical history, full physical examination (including vital signs), 12-lead ECG and clinical laboratory tests. They could weigh no more than 200 lbs. and had to be within 15% of their weight range for age, gender, height and frame pursuant to the 1983 Metropolitan Life Insurance Height and Weight Tables. The following laboratory parameters had to be within the reference range: WBC, absolute neutrophil count, hemoglobin, and hematocrit. Albumin could not be less than the lower limit of the reference range. The following laboratory parameters could not be greater than the upper limit of the reference range: BUN, creatinine, AST (SGOT), ALT (SGPT), alkaline phosphatase, and total bilirubin. . The values for a urine drug screen, serum pregnancy test (female subjects), salicylate screen, and urine cotinine test were required to be negative.

Women of child-bearing were required to use one of a list of suitable measures to prevent conception for at least 3 months prior to the study. Breast-feeding women could not be enrolled.

Subjects who failed to complete the study could be replaced.

**Results**

Of the original 16 patients who enrolled, all but one completed the study. One subject randomized to placebo withdrew consent on Day 2 due to a family emergency. This subject was replaced with a placebo arm subject who completed the study. Thus, 17 subjects were enrolled and analyzed for safety and 16 (8 in each arm) completed the study and were analyzed for the various PD assessments.

Results for the various assessments of TXB\textsubscript{2} are shown in Table 6. Results for inhibition of TXB\textsubscript{2} and platelet aggregation after an aspirin dose are similar in the celecoxib and placebo arms. Inhibition of TXB\textsubscript{2} generation was ~99% in each arm, with very little variability. These results suggest that administration of celecoxib 200 mg bid for 4.5 days had no notable effect on aspirin-induced platelet inhibition.

Table 7 shows values for TXB\textsubscript{2} at Hours 0, 2, and 8 on Day 5. The Hour 8 values are the same as in Table 6. Values at all time points on Day 5 are not significantly different between the arms, but there was somewhat more inhibition of TXB\textsubscript{2} at Hour 0 (the time of aspirin dosing) with celecoxib compared to placebo, suggesting the possibility of modest celecoxib-induced inhibition of TXB\textsubscript{2} generation after 4 days of bid dosing. However, the effect of aspirin on any platelet function parameter was not diminished in the celecoxib arm on Day 5.
We also did our own analysis of TXB₂ inhibition at Day 5, Hour 8 (the final value), using data listings in the study report and focusing on individual results. The results are shown in Table 8. Results for the mean, SD, minimum value and maximum value in the two arms are similar. Of note, the minimum values for percent inhibition in the placebo and celecoxib arms were 98.1 and 97.8, respectively, meaning that every patient in each arm had nearly-complete inhibition of TXB₂ production.

Table 6 Study N49-01-06-150: Final %TxB2 and Platelet Aggregation Inhibition Variables

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo N=8</th>
<th>Celecoxib 200 mg BID N=8</th>
<th>Ratio (%) or Difference Least Squares Means</th>
<th>Ratio (%) or Difference 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>% TxB2 Inhibition</td>
<td>99.36</td>
<td>99.01</td>
<td>99.65</td>
<td>(99.03, 100.27)</td>
</tr>
<tr>
<td>% Inhibition of Platelet Aggregation due to ADP</td>
<td>18.67</td>
<td>16.31</td>
<td>-2.36</td>
<td>(-17.22, 12.50)</td>
</tr>
<tr>
<td>% Inhibition of Platelet Aggregation due to Collagen</td>
<td>74.19</td>
<td>83.85</td>
<td>113.01</td>
<td>(86.87, 147.02)</td>
</tr>
<tr>
<td>% Inhibition of Platelet Aggregation due to Arachidonic Acid</td>
<td>93.93</td>
<td>95.24</td>
<td>101.40</td>
<td>(98.87, 103.99)</td>
</tr>
</tbody>
</table>

% TxB₂, platelet aggregation due to collagen or arachidonic acid: logarithmic least squares means back-transformed to the original scale.

For %TxB₂, platelet aggregation due to collagen or arachidonate, the ratios of the least squares means are presented as celecoxib/placebo. For platelet aggregation due to ADP, the difference in least squares means is presented as celecoxib-placebo.

Note: "Final" values are based on blood drawn 8 hours after aspirin dosing on Day 5.
Source: CSR Table 8.b

Table 7 Study N49-01-06-150: %TxB2 Inhibition on Day 5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo N=8</th>
<th>Celecoxib 200 mg BID N=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>% TxB2 Inhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hour 0</td>
<td>19.20</td>
<td>35.41</td>
</tr>
<tr>
<td>Hour 2</td>
<td>99.70</td>
<td>99.64</td>
</tr>
<tr>
<td>Hour 8</td>
<td>99.36</td>
<td>99.01</td>
</tr>
</tbody>
</table>

Note: Hour 8 values are similar to those in the Table 6.
Source: CSR Table 8.c

It probably was not important that in this study, immediate release aspirin was used, because aspirin and celecoxib were given at the same time, 12 hours after the previous dose of celecoxib. However, the dose of aspirin, 325 mg, was 4 times the usual CV prevention dose in

Consult: Pharmacodynamic interactions of aspirin with ibuprofen or celecoxib

Reference: 4140757
the US of 81 mg. It is possible that a lower dose of aspirin might have been associated with a modest interaction with celecoxib. Nevertheless, any interaction with celecoxib is still not expected to last beyond the initial few days upon low-dose aspirin initiation, because aspirin at 81 mg is still more than what is required to cause maximal inhibition of serum TxB2 (7). Also, for the same reason, we might not expect any meaningful interaction in a scenario where celecoxib is initiated in a patient on chronic low-dose aspirin.

Table 8 Study N49-01-06-150: Final %TxB2 Inhibition  
(Reviewer’s Analysis)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo N=8</th>
<th>Celecoxib 200 mg BID N=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>99.5</td>
<td>99.0</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.57</td>
<td>0.80</td>
</tr>
<tr>
<td>Min</td>
<td>98.1</td>
<td>97.8</td>
</tr>
<tr>
<td>Max</td>
<td>99.9</td>
<td>99.9</td>
</tr>
</tbody>
</table>

Source: CSR Appendix 3.6.1: List of TxB2 Levels and % inhibition

3.3 Overall Assessment

Celecoxib 400 mg bid did not affect collagen-induced platelet aggregation in the study by Simon et al. The interaction between celecoxib and aspirin was not assessed in this study. However, in the study performed by Searle, celecoxib at a dose of 200 mg q 12 hours for 4.5 days did not interfere with inhibition of COX-1 by aspirin 325 mg given at the same time as the last dose of celecoxib. In the absence of clinical data, a modest interaction with low-dose aspirin when initiated on a background of celecoxib cannot be ruled out. The extent of any interaction with low-dose aspirin (if exists) could be determined via a clinical drug interaction study designed similarly to the study performed by Searle but randomizing patients on celecoxib to repeat doses of low- and high-dose aspirin and measuring the time-courses for serum TxB2 and arachidonic acid induced platelet aggregation before and after aspirin treatment.
INDICATIONS

**OTC Ibuprofen sodium:**

Temporarily relieves minor aches and pains due to:
- headache
- toothache
- backache
- menstrual cramps
- the common cold
- muscular aches
- minor pain of arthritis

Temporarily reduces fever

**Prescription strength ibuprofen: (200, 300, 400, & 800 mg IR tablets)**

Ibuprofen tablets are indicated for:
- relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis,
- relief of mild to moderate pain, and
- the treatment of primary dysmenorrhea.

**Celecoxib:**

Celecoxib is indicated for the management of:
- the signs and symptoms of osteoarthritis
- the signs and symptoms of rheumatoid arthritis
- the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older
- the signs and symptoms of ankylosing spondylitis
- acute pain in adults, and
- primary dysmenorrhea

REFERENCES


This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUDHARSHAN HARIHARAN
08/21/2017

MEHUL U MEHTA
08/22/2017

MARTIN ROSE
08/22/2017

NORMAN L STOCKBRIDGE
08/22/2017
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products  
Medical Reviewer Consult TSI-490

DATES:  
Consult Request Date: May 23, 2016  
Requested Completion Date: July 28, 2016  
Consult Completion Date: August 8, 2016

FROM:  
Preston M. Dunnmon, M.D., Medical Officer  
Division of Cardiovascular and Renal Products, HFD-110

THROUGH:  
Norman Stockbridge, M.D., Ph.D., Division Director  
Division of Cardiovascular and Renal Products, HFD-110

SUBJECT:  
TSI # 490, the naproxen-aspirin interaction

SPONSOR:  
Bayer

NAME OF DRUG:  
Naproxen Sodium IR 220 mg

FORMULATION:  
Tablet

RELATED APPLICATIONS:  
IND 74,293, IND 31391, NDA 20-204

DEVELOPMENT INDICATION:  
Minor aches and pains associated with head, back,  
and muscular aches, the common cold and toothache, the minor pain of arthritis, the pain  
of menstrual cramps, and the temporary reduction of fever

DOCUMENTS AVAILABLE FOR REVIEW:  
Medical Officer Review (22 September 2006)  
Medical Officer Review (13 March 2008)  
Medical Officer Review (8 September 2009)  
Advice Letter to Bayer (2 April 2010)  
General Correspondence from Bayer (16 November 2010)  
DCRP Consult (30 Mar 2011)  
DCRP Consult (28 June 2011)  
Advice Letter IND 74293 (5 July 2012)  
DCRP Consult (25 June 2013)  
Trial 15525 Clinical Study Report
**Consult Question**

Bayer, the sponsor of the OTC naproxen product (Aleve), has completed trial 15525 that demonstrates an interaction between naproxen and aspirin such that aspirin’s effect on platelet aggregation inhibition is diminished under certain conditions. Bayer is considering inclusion of this information in the Drug Facts Label (DFL) of Aleve and has sought FDA input on how the information should be included. The sponsor has recently posted summary results of Study on clintrials.gov. The Division of Nonprescription Drug Products intends to move forward with labeling the OTC naproxen products for this interaction; however, the advice in the DFL will likely be very general. DAAAP will need to label the same interaction in all prescription naproxen products via a FDAAA safety labeling change, and provide more detailed information about the effect of the interaction on platelet aggregation because such information will not be in the DFL. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requests input on labeling this issue from the Division of Cardio Renal Products (DCRP).

**Background**

Non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase-1 (COX-1) prevent the conversion of arachidonic acid (AA) to thromboxane, thereby blocking thromboxane-induced platelet aggregation. It is by this mechanism that COX-1 inhibiting NSAIDs prevent cardiovascular (CV) events in vulnerable individuals (FDA Science Paper on interaction between low dose aspirin and OTC doses of ibuprofen).

Aspirin is an irreversible inhibitor of COX-1 as a result of its acetylation of Ser529 (thereby preventing AA from contacting Tyr385). All other NSAID inhibitors of COX-1 are reversible inhibitors of this enzyme. Propionic acid-derived non-aspirin NSAID inhibitors of COX-1, such as ibuprofen and naproxen, are thought to bind reversibly to the same platelet binding site that aspirin acetylates (Ser529). While platelet bound, ibuprofen and naproxen confer an antiplatelet effect. However, because they are reversibly bound (i.e. disassociate from the platelet as their serum concentration falls), it is possible that they interfere with the permanent antiplatelet effect of aspirin by leaving unacetylated platelets behind as they dissociate from their platelet binding sites.

This effect has been shown in human ex vivo studies with ibuprofen that demonstrate an ibuprofen-induced attenuation of the expected aspirin-mediated irreversible inhibition of thromboxane B2 (TXB2) production as well as an attenuation of the consequent aspirin-mediated attenuation of platelet aggregation. Accordingly, dosing recommendations to take immediate release aspirin at least 30 minutes before ibuprofen have been made so as to avoid the ibuprofen-aspirin interaction.

Mechanistically, it would be reasonable to expect that naproxen would demonstrate a similar interference with low-dose aspirin taken to prophylax the occurrence of CV events in vulnerable individuals, but the timing of the demonstrated interaction could be reasonably expected to differ from the ibuprofen interaction with low-dose aspirin due to
naproxen’s longer half-life. The data supporting this hypothesized naproxen-aspirin (NAP-ASA) interaction has been building slowly over the past years.

No studies with clinical cardiovascular outcome endpoints have been conducted with either ibuprofen or naproxen to confirm the theoretical consequences of this loss of platelet inhibiting effect of aspirin in vulnerable patients.

There were at least three Divisional MO reviews of this topic between 2006 and 2009, following which there have been 3 DCRP consults between 2008 and 2013 regarding the Agency’s concern about this potential interaction, along with multiple communications with Bayer over these years regarding the design of a study that would be sufficiently rigorous and have the capability of resolving an ASA-NAP interaction. With the recent completion of Bayer’s trial 15525, ex-vivo interference by naproxen with the expected aspirin-mediated permanent inhibition of thromboxane generation and platelet aggregation has now been unequivocally demonstrated.

The following sections of this review summarize key data that elicited the concern about a potential NAP-ASA interaction, DCRPs interpretation of these data and the joint DCRP-OCP consultative assessments and recommendations over the years that led to the completion of trial 15525, the key results of trial 15525, and DCRP’s assessments and recommendations regarding the communication of these results to health care providers through direct communications and through labeling. In each of the following summary sections, the complete consults and advice letters from which the summaries have been generated are embedded to the Word version of this review for reference if needed, and linked to the PDF version of this review in DARRTS.

**DCRP Consults 2011**

Based on extensive literature reviews and three separate medical officer (MO) reviews in 2006, 2008, and 2009, FDA was concerned that there exists an interaction between aspirin (ASA) and naproxen (NAP) that may at least in part nullify the protective effect of low dose ASA taken once daily for cardiovascular and cerebrovascular protection in at-risk patients. In this regard, NAP had been shown to have intrinsic platelet inhibitory activity as measured by the inhibition of thromboxane B2 (TXB2) production and subsequent platelet aggregation when used in high split dosing regimens that are typical of the prescription product. However, short intermittent courses of the low dose OTC product may result in NAP washout, leaving unacetylated, activatable platelets in the circulation that could result in negative cardiovascular outcomes. This concern was based on the work of Capone et al. (Table 1, % Inhibition of TXB2) and Patrignani’s reanalysis of older Capone studies (Fig 1, TXB2 Concentration) as follows:
Table 1: Thromboxane inhibition at time points following the final dose after 6 days of dosing with naproxen sodium 220 mg and 440 mg twice daily (from Capone et al, 2007)

<table>
<thead>
<tr>
<th>Time</th>
<th>% Thromboxane Inhibition ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Naproxen sodium 220 mg BID (n=6)</td>
</tr>
<tr>
<td>2 h</td>
<td>95.9 ± 5.1</td>
</tr>
<tr>
<td>5 h</td>
<td>90.8 ± 8.6</td>
</tr>
<tr>
<td>8 h</td>
<td>88.9 ± 10</td>
</tr>
<tr>
<td>12 h</td>
<td>86.6 ± 7.1</td>
</tr>
<tr>
<td>24 h</td>
<td>69.1 ± 19.9</td>
</tr>
</tbody>
</table>

SD= standard deviation, BID=twice daily

Figure 1: Serum TXB2 levels over time compared with drug administered, 100 mg ASA or 500 mg NAP alone, and ASA before or after NAP

Consequently, FDA issued an advice letter to the sponsor dated 2 April 2010 requesting a study that was appropriately designed either to rule out or to delineate an important low-dose-ASA – low-dose-NAP pharmacodynamic interaction that might impact the cardiac safety of patients receiving both drugs.
Subsequent to FDA’s April 2, 2010 Advice letter to the Sponsor, Anzellotti et al published a paper in which the potential for an interaction between 100-mg IR QD ASA and 220-mg IR BID NAP was assessed in a 3 period cross-over study of 9 healthy subjects (Arthritis & Rheumatism 2011;63(3):850–59). The major findings of this small study included the following:

1. Platelet COX-1 activity ex vivo (reported as the percent of inhibition [% I]), as assessed by the measurement of serum thromboxane B₂ (sTXB₂), was decreased at 24 hours (after the first drug was given) when NAP was dosed 2 hours before ASA, but not when ASA was dosed two hours before NAP, as compared to ASA alone (see Figure 1 from that paper below).

![Figure 1](image-url)
2. Low-dose aspirin alone caused a significant inhibition of collagen-induced platelet aggregation up to 48 hours after dosing, although heterogeneity of the response was detected. In contrast, collagen-induced platelet aggregation rapidly recovered after the sequential administration of aspirin and naproxen (in both directions; see Figure 2 panel C from that paper below).

Figure 2. Inhibition of platelet function ex vivo by administration for 6 days of naproxen sodium (220 mg twice a day) 2 hours before aspirin, naproxen sodium 2 hours after aspirin, or low-dose aspirin alone. Platelet aggregation was assessed by measuring the percent of inhibition (% I). Data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and the whiskers represent the highest and lowest values. Open symbols represent individual values. A, Platelet aggregation induced by 2 mM arachidonic acid (AA). At each time point after dosing with the 3 different treatments, platelet aggregation was significantly reduced compared with predrug values (*** = $P = 0.0001$). # = $P = 0.0053$ versus aspirin alone at 48 hours. B, Platelet aggregation induced by 1 mM AA. At each time point after dosing with the 3 different treatments, platelet aggregation was significantly reduced compared with predrug values (*** = $P = 0.0001$), $\$ = P = 0.0001$ versus aspirin before naproxen at 24 hours, $\# = P = 0.016$ versus aspirin alone at 48 hours, $\dagger = P = 0.0003$ versus aspirin alone at 24 hours. $\phi = P = 0.04$ versus aspirin alone at 48 hours. C, Platelet aggregation induced by 10 µg/ml collagen. $\ast\ast = P = 0.0001$ versus predrug values. $\Phi = P = 0.0005$ versus aspirin alone at 24 hours. $\dagger\dagger = P = 0.0013$ versus aspirin alone at 48 hours. $\#\# = P = 0.0045$ versus predrug values. $\$\$ = P = 0.01$ versus predrug values. $@ = P = 0.0005$ versus aspirin alone at 48 hours. $* = P = 0.0003$ versus predrug values. For this statistical analysis we used mixed-effects model procedures and nonparametric bootstrap resampling technique (35). WO = washout.
3. The sequential administration of naproxen and aspirin (in both directions) did not substantially affect the inhibition of the urinary excretion of TX-M caused by aspirin alone (see Figure 3 from that paper below).

![Figure 3](image-url)

Figure 3. Comparison of the degree and duration of steady-state inhibition of thromboxane A₂ (TXA₂) biosynthesis in vivo by administration for 6 days of naproxen sodium (220 mg twice a day) 2 hours before aspirin, naproxen sodium 2 hours after aspirin, or low-dose aspirin alone. Urinary excretion of 11-dehydro-TXB₂ (TX-M; an index of TXA₂ biosynthesis in vivo), reported as the percent of inhibition (% I), was detected after dosing with the 3 different treatments. Data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and whiskers represent the highest and lowest values. Open symbols represent individual values. At each urine collection obtained after dosing with the 3 different treatments, urinary excretion of TX-M was significantly reduced compared with predrug values (\(* * = P = 0.0001\)). § = $P = 0.049$ versus aspirin alone at 12–24 hours. \# = $P = 0.037$ versus aspirin alone at 6–12 hours. For this statistical analysis we used mixed-effects model procedures and nonparametric bootstrap resampling technique (35). WO = washout.
4. In a subset of 5 patients, the authors compared the rate of biosynthesis of TXB2 in platelet-rich plasma stimulated with AA and collagen and in serum up to 72 hours after discontinuation of the different treatments by assessing the slope and y-intercept values of the least squares lines (using simple linear regression analysis) describing the relationship between TXB2 biosynthesis and time. The authors concluded that “…the assessment of TXB2 generation in the presence of 10 microgram/ml collagen was more appropriate than the other biomarkers to detect a pharmacodynamic interaction between aspirin and naproxen.” (See Figure 4 from that paper below).

From these data, DCRP assessed and recommended the following in 2011:

DCRP Assessments (2011)

1. The work by Anzellotti et al as outlined above could be the basis for labeling IR 220-mg NAP for an ASA interaction requiring dosing of IR NAP 2 hours following IR ASA, with a modeling-based recommendation for the period of time that NAP dosing could precede ASA dosing. However, a trial as outlined is still preferable because:
a. The doses of both ASA (100 mg QD) and NAP (220 mg BID) in this study are higher than the doses of interest to FDA for ASA and NAP (81 mg and 220 mg QD, respectively).

b. It is possible that the low dose 220-mg QD NAP dose may produce even more worrisome results due to a reduction in NAP-mediated platelet inhibition relative to the higher NAP dose used in the Anzellotti study.

c. At this point, it is unclear whether the labeling should state that dosing ASA two hours before NAP abolishes the interaction risk, or simply reduces its magnitude due to the evidence from the Anzellotti study of loss of inhibition of COX-1 activity in the collagen-stimulated platelet aggregation assay and possibly the collagen-stimulated TBX2 assay as well.

d. A clinical trial as suggested is the only way for a sponsor(s) to demonstrate that 6 days of pre-treatment with 81-mg IR ASA QD may prevent the loss of COX-1 inhibition that is demonstrated in the Anzellotti study at 24 hours in the various assays described above.

2. The most scientifically pure approach to this question would be a large cardiovascular outcomes study. However, we do not anticipate that this approach would be possible to execute successfully for an OTC medication being given in short (less than 10-day) bursts for transient pain indications (as opposed to a drug that the patient would take every day over a long period of time). Thus, we agree that the PD approach is the most pragmatically executable approach, though the sponsor’s assertion that % TXB2 inhibition is a recognized surrogate for CV clinical outcomes is overstated.

3. All FDA requested design elements that were enumerated in the April 2, 2010 advice letter have been incorporated into the study protocol with respect to ASA formulation, ASA dose, NAP dose, and the timing and order of ASA and NAP administration. The OCP reviewer is satisfied with the overall protocol design from this perspective (see OCP review attached, pages 14 – 16 below).
4. We understand that the sponsor is excluding any subject with a ≤ 95% inhibition of TXB2 synthesis on Day 7 (following a six day run in period with daily dose 81 mg IR ASA) for two reasons: to reduce variability and/or confounding by eliminating 1) subjects who were either non-compliant with their ASA run-in dosing as outpatients during days 1-6 prior to the inpatient treatment period (days 7-17), or 2) subjects who are ASA resistant.

In a prior study examining these same issues with NAP 220 mg PO TID, study BAY 126112, 80% of the subjects had > 95% sTXB2 inhibition on day 6 (end of the ASA run-in period). Of the 9 individuals who had < 95% sTXB2 inhibition on day 6 who had follow up data, all of them showed an increased TXB2 inhibition when either NAP or acetaminophen (APAP) was added to ASA (3/9 were randomized to receive APAP, 8/9 had %TXB2 inhibition increase to 99% and 1/9 had an increase to 92%). Some of these increases were statistically overwhelming (one person with a % TXB2 inhibition on day 6 of 0.2% increased to 99.9% inhibition of TXB2 on day 11). Of note, all of these patients were considered non-evaluable due to the confounding influence of their sometimes huge increases in % TXB2 inhibition. This huge increase would likely have obscured smaller decreases in % TXB2 inhibition that the study was seeking to demonstrate as a consequence of an anticipated ASA – NAP interaction.

However, there is a possibility that patients with true ASA resistance, if separated out from patients who are simply non-compliant during the ASA run-in phase, could demonstrate an exaggerated negative interaction with low dose NAP with respect to TXB2 inhibition and platelet aggregability. Furthermore, it is possible to separate resistant patients from non-compliant patients by several relatively simple trial design maneuvers which could include, but are not necessarily limited to:

- Requiring patients to report to the study center daily, as outpatients, during the days 1-6 ASA run-in period so that they could be administered their 81 mg IR ASA in a witnessed fashion, or
• Measurement of salicylate levels on day 7 prior to the initiation of the study treatment phase.

5. We do not agree that the sponsor has made a convincing case for selecting 90% inhibition of TXB2 as the allowable lower bound of the 95% CI for claiming no relevant interaction between ASA and NAP. The 5% variability that the sponsor notes for day to day variation of TXB2 measurements (implicitly from the same person) is an issue driving sample size, not the lower bound of the allowable margin of the primary efficacy endpoint.

The sponsor’s own reference (Reilly, 1987) concludes that “Lesser degrees of (thromboxane) inhibition (95% or lower) would not be expected to substantially influence thromboxane-dependent platelet activation in vivo.” It is further noted that the large majority of patients from the sponsor’s BAY 12611 study demonstrated a \( \geq 98\% \) TXB2 inhibition after six days of EC ASA 81 mg QD. Therefore, the clinically relevant population for the primary endpoint assessment would be the patients with \( \geq 98\% \) inhibition of TXB2 on day 7, with no PD interaction claimed if the lower bound of the one-sided 95% CI that is constructed for serum TXB2 inhibition at Hour 24 on Day Final is greater than 95% for all treatment groups (as opposed to any of the groups, as is written in the current protocol).

6. ASA resistant patients, identified as outlined in “3” above, should be analyzed separately as a secondary endpoint (all analyses).

7. Given the expectation that an ASA/NAP interaction will be most prominently demonstrated with NAP given 30-120 min prior to ASA dosing, the primary PD parameter should be TXB2 inhibition at Hour 24 on Day Final in Group 2 (as currently defined, NAP 220 mg 30 minutes before IR ASA), and would recommend extending the dosing interval to 2 hours, considering the variability in achieving peak NAP serum concentrations.

8. Combining the concerns as stated in items 3 – 5 above, we believe that 10 evaluable patients per arm is not sufficient. Based on the above mentioned items, the sponsor should calculate and justify sample sizing for this trial and submit this information to FDA for concurrence. An estimate of the number of ASA resistant patients (not the combination of resistance and non-compliance) should be made and justification given for the expected numbers of these patient to be included in the study (which will be derived from the anticipated percent of these specific patients in the overall population to be enrolled).

9. The analytical plan for the day 17 urine collection should be delineated in the protocol (is this being used to assess thromboxane urinary metabolites?)
10. For the light transmission aggregometry (LTA) assay, we would expect to see a sigmoid shaped curve, as opposed to the all or nothing type result that has been noted in prior references from MO reviews that might suggest assay sensitivity limitations of the platelet aggregation assay. Data from Anzellotti et.al. (Arthritis & Rheumatism, March 2011) suggest that a platelet aggregation assay based on induction by 10 microgram/ml collagen is a more sensitive assay that assays based on AA induction of platelet aggregation. Platelet aggregation should be measured by both methods.

11. Data from Anzellotti et.al. (Arthritis & Rheumatism, March 2011) also suggests that TBX2 generation from collagen-stimulated platelet-rich plasma may be a more sensitive assay for small changes in COX-1 inhibition than serum TBX2 levels. TBX2 should be measured by both methods.

DCRP-OCP Recommendations for Trial 15525 Design (2011)

It is the recommendation of both OCP and DCRP that the originally proposed trial by the sponsor (reflecting FDA’s advice letter) be modified as follows:
• **Group 1** – ASA and NAP given concomitantly
  o maintain as proposed
  o represents the reality that these drugs are frequently taken together
• **Group 2** – NAP 30 min before ASA
  o maintain as proposed
  o Functions as positive control for the trial to ensure assay sensitivity
• **Group 3** – NAP administered 8 – 12 hours before ASA
  o Additional arm
  o addresses the question regarding how many hours after an NAP dose that ASA can be taken without loss of platelet inhibition
• **Group 4** – ASA alone
  o Maintain as proposed
  Functions as negative control for the trial

Trial 15525 should be considered positive for an ASA-NAP interaction if any of the test arms demonstrate the interaction, though the primary PD assessment group should be the additional group 3 (NAP 8-12 hours before ASA), given that the primary question of interest to the agency at this point is the amount of time following NAP that ASA can be given without loss of anti-platelet effect.

2. DCRP concurs with the OCP reviewer’s recommendation with respect to preference for AA stimulation in the platelet activation assays as opposed to the use of collagen in concentrations that stimulate platelets via non-AA mediated pathways.

3. Enroll patients into the treatment period with ≥ 98% TXB2 inhibition on day 7, with no PD relevant interaction claimed if the lower bound of the one-sided 95% CI that is constructed for serum TXB2 inhibition at Hour 24 on the Final Day of dosing is greater than 95% for all treatment groups (as opposed to any of the groups, as is written in the sponsor’s proposed protocol).

4. Recalculate sample size based on above parameters, considering 5% day to day variability of the TXB2 assay that the sponsor notes, with estimation/justification of the number of ASA resistant patients that will be expected in the secondary analysis based on the revised overall sample sizing for the primary PD analysis. The assumed day to day variability of the TBX2 assay may change if a collagen-stimulated platelet-rich plasma assay is incorporated into the trial.

5. Modify the protocol to identify ASA resistant patients (as opposed to non-compliant patients) following the days 1-6 ASA run-in, and include them in the trial as noted above.
6. Analyze ASA resistant patients separately as a secondary endpoint (all analyses).

7. Delineate what urinary-metabolic testing is planned.

8. Maintain planned secondary analyses of PD parameters as delineated in the current protocol (TXB2 inhibition on the Final Day of dosing at all other time points except 24 hours and on Day 7 at all time points and inhibition of platelet aggregation on Days 7 and Final at all time points).

**FDA Advise Letter to Sponsor (2012)**

Following the communication of the above (2011) recommendations from DCRP-OCP to Bayer, the sponsor submitted the following questions to FDA in 2012, to which FDA responded, communicating FDA’s ongoing disagreement with Bayer’s preferred inclusion criterion for baseline %TXB2 inhibition, as well as the rather broad definition that was planned for determining no interaction between NAP and ASA, as noted below:

1. Does the FDA agree with the proposal to extend the ASA alone treatment by three days for all of the treatment groups?

   *FDA Response: Yes, we agree.*

2. Does the FDA agree to the addition of the following group: NAP 220 mg administered 30 min before ASA and a second dose of NAP 220mg administered 12 hours later?

   *FDA Response: Yes, we agree. Additionally, in order to maximize information collected in this treatment arm, consider modifying the sampling schedule (in this treatment arm) to include sampling times post administration of the second dose of NAP 220 mg.*

3. Does the FDA agree that adding subjects with "resistance to aspirin" is not useful in meeting the study’s objective and that provisions to identify and separate ASA resistant patients will not be included in this study?

   *FDA Response: We disagree with your premise that identifying and characterizing the potential NAP-ASA interaction in poor ASA responders would not be a useful endeavor. However, we suspect (based on your prior experience that was provided in previous submissions) most of these cases represent poor compliance with ASA dosing on an outpatient basis as opposed to aspirin*
resistance. In study BAY 126112, of the 9 individuals with follow-up data who had < 95% sTXB2 inhibition on day 6, all showed an increased TXB2 inhibition when either NAP or acetaminophen (APAP) was added to ASA. Some of these increases were statistically substantial. (One person with a 0.2 % TXB2 inhibition on day 6 had an increase of TXB2 inhibition to 99.9% on day 11). Of note, all of these subjects were considered non-evaluable due to the confounding influence of their substantial increases in % TXB2 inhibition. This substantial increase would likely have obscured smaller decreases in % TXB2 inhibition that the study was seeking to demonstrate as a consequence of an anticipated ASA – NAP interaction.

Therefore, we agree with your plan not to separate/identify poor ASA responders, if you allow only those subjects who achieve 98% TXB2 inhibition at the end of the ASA run-in to proceed on to the treatment period of your study.

4. Does the FDA agree that the use of 95% TXB2 inhibition level is appropriate as an enrollment criterion?

FDA Response: No, we do not agree. Data from Anzellotti et al. (Arthritis & Rheumatism, March 2011) demonstrate that 98% inhibition of TXB2 production should be achievable in most patients. We also note that the large majority of participants from your BAY 12611 study demonstrated a > 98% TXB2 inhibition after six days of EC ASA 81 mg QD. Furthermore, your reference from Reilly, 1987, concludes that, “Lesser degrees of (thromboxane) inhibition (95% or lower) would not be expected to substantially influence thromboxane-dependent platelet activation in vivo.” Therefore, the clinically relevant population for the primary endpoint assessment would be those people with > 98% inhibition of TXB2 on day 7. There would be no PD interaction claimed if the lower bound of the one-sided 95% CI that is constructed for serum TXB2 inhibition at Hour 24 on the final day of dosing is greater than 95%.

5. Does the FDA agree that 90% as the lower bound limit of the one-sided 95% CI for TXB2 inhibition at 24 Hour on the final day of dosing represents clinically relevant inhibition of platelet aggregation?

FDA Response: No, we do not agree. See the response to question 4. In addition, please note that the 5% variability that you report for day-to-day variation of TXB2 measurements (implicitly from the same person) is an issue that impacts sample size, not the lower bound of the allowable margin of the primary efficacy endpoint.

6. Does the FDA agree with Bayer’s proposal that if no PD relevant interaction is shown for Group 2 in the primary analysis (> 90% TXB2 inhibition), no PD interaction will be claimed for the other treatment groups if each treatment group demonstrates > 90% TXB2 inhibition; and that all analysis results will be presented for complete assessment and interpretation?
FDA Response: We agree with your plan to assess each treatment group for TXB2 inhibition. We do not agree on the > 90% lower bound limit for the treatment effect, per our response to question 4.

DCRP Consult (2013)

After communication of DCRP’s responses to the sponsor’s 2012 questions via and advice letter, another year passed and DCRP was again consulted to address Bayer’s ongoing objections to the criteria that DCRP recommended both for baseline %TXB2 inhibition following the ASA run-in, as well as the acceptable lower limit of TXB2 following NAP administration for which “no-interaction” could be claimed. The company’s position in 2013 was stated as follows:

There is no gold standard identified in the scientific literature for the use of > 90% or 95% as the threshold for the lower bound of the one-sided 95% CI for serum thromboxane B2 (TxB2) inhibition to achieve the clinical benefit of platelet inhibition-derived prevention of secondary cardiovascular event. Bayer believes that > 90% is the appropriate threshold for the lower bound. Given the lack of clear evidence in the scientific literature, does the Agency agree that a > 90% lower bound of the one-sided 95% CI for the serum TxB2 inhibition may be used to claim no clinically-meaningful pharmacodynamic interaction of naproxen therapy with aspirin therapy?

After an extensive a thorough literature review of this subject, DCRP remained convinced that the inclusion criterion and “no-interaction” criterion that it had proposed were correct and the use of these thresholds would improve the ability of proposed trial 15525 to resolve the presence of an NAP-ASA interaction. The Division again concluded that, “Assessment of TxB2 inhibition as a surrogate to support a labeling claim of “no relevant PD interaction” between NAP and ASA will necessitate a rigorously acquired, robust dataset, using contemporary measurement technologies. The cutoff criteria that the agency has proposed has been demonstrated to be achievable (in the sponsor’s data as well as in the published data), and it will be compelling.”

Trial 15525 Final Study Report and Review (2016)
Trial 15525 Design

This was a randomized, controlled, open-label, parallel-group study to determine the effects on platelet inhibition when OTC naproxen sodium 220 mg was added to low-dose, IR ASA therapy that consisted of three periods as follows:

1. Run-In Period (study days 1-6)
   a. A baseline blood sample for TXB2 level and arachidonic acid (AA)-induced platelet aggregation were taken prior to dosing.
   b. Subjects were administered their first dose of IR ASA 81 mg once daily (qd) at the clinical study site.
   c. To ensure compliance, subjects were instructed to return to the clinical study site on Days 4 to 6, for site staff to observe dosing at the target dosing time.

2. Treatment Period (study days 7-16)
   a. Subjects who demonstrated a minimum Day 1 (baseline) TXB2 value of 5000 pg/mL and <20% AA-induced platelet aggregation on Day 7 were randomized to 1 of 6 treatment groups and were administered their assigned treatment daily for 10 consecutive days by the clinical study site staff.
   b. On Day 7, subjects not demonstrating ≥98% serum TXB2 inhibition were not included in the evaluable population (serum TXB2 results were available after the subjects were randomized; these subjects were not withdrawn from the study but were deemed non-evaluable).
   c. Subjects were sequestered at the clinical study site for a total of 14 days (all of the Treatment Period and all of the Run-Out Period).
   d. A blood sample to assay TXB2 levels and AA-induced platelet aggregation after 6 days of IR ASA treatment during the Run-In Period was taken within approximately 2 hours prior to first dosing in the Treatment Period.
   e. Investigational product was administered by the clinical study site staff while subjects were sequestered.
   f. Blood samples were obtained on study days 7 and 16 at 1, 3, 6, 12, 18, and 24 hours postdose, relative to the time of IR ASA 81 mg administration.

3. Run-Out Period (study days 17-19)
   a. IR 81mg ASA only was continued as it was administered in the Treatment Period, but all NAP discontinued.
   b. Blood samples were obtained on study days 17 and 19 at 1, 3, 6, 12, 18, and 24 hours postdose, relative to the time of IR ASA 81 mg administration.

Summary of PD Assessments

Blood draws for PD assessments were performed at predose on Days 1 and 7 and postdose on Days 7, 16, 17, and 19 at 1, 3, 6, 12, 18, and 24 hours relative to the time of IR ASA 81 mg administration.
The Study schematic is as follows (from page 23/3119 of the trial 15525 FSR):

As shown in the schematic, the final treatment period groups that the sponsor tested in trial 15525 were as follows (with DCRP interpretation of what each study arm will show in italics):

- **Group 1** – 10 days of ASA (IR 81 mg) and NAP (220 mg QD) given concomitantly
  - represents the reality that these drugs are frequently taken together
- **Group 2** – 10 days of NAP (220 mg QD) 30 min before ASA
  - Functions as positive control for the trial to ensure assay sensitivity if an interaction does indeed exist
- **Group 3** – 10 days of NAP (220 mg QD) administered 8 hours before ASA
  - addresses the question regarding how many hours after an NAP dose that ASA can be taken without loss of platelet inhibition
- **Group 4** – 10 days of ASA alone
  - Functions as negative control for the trial
- **Group 5** – ASA administered 30 min before NAP (220 mg QD)
  - addresses the question regarding how many hours after an NAP dose that ASA can be taken without loss of platelet inhibition, as well as the question as to whether NAP administered after ASA interferes with ASA’s antiplatelet effect
• Group 6 – 10 days of NAP (220 mg bid 12 hours apart) where first dose is 30 minutes before IR ASA 81 mg qd
  o DCRP would anticipate this BID dosing regimen as a worst case scenario for an interaction if one does indeed exist.

Trial 15525 Key Inclusion Criteria

• Healthy, ambulatory, male and female volunteers between 18 to 70 years of age with a body mass index (BMI) of approximately 18 to 30 kg/m2, and a total body weight ≥50 kg (110 lbs.)
• Results of Screening and clinical laboratory tests were within normal range or considered not clinically significant by the Principal Investigator and the Sponsor

Trial 15525 Key Exclusion Criteria

• Eighteen to twenty year olds with a viral infection, with or without fever within 1 month prior to start of Run-In Period
• History of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Active, or history of recurrent peptic ulcer/hemorrhage (2 or more distinct episodes of proven ulceration or bleeding)
• Had taken any medications including NSAIDs (except acceptable forms of birth control) within 7 days prior to the start of the Run-in Period or throughout the study, unless in the opinion of the Investigator and the Sponsor, the medication did not interfere with the study procedures, data integrity, data interpretation, or compromise the safety of the subject
• Any vitamin or herbal supplement within 7 days prior to the start of the Run-In Period or refused to refrain from use during the study
• Antiplatelet or anticoagulant drugs within 30 days prior to start of the Run-In Period or during their participation in the study
• Smokers or anyone who consumed any type of nicotine or tobacco products (e.g., chewing tobacco, electronic cigarettes, nicotine replacement therapy)
• Positive test for drugs, alcohol, and cotinine

Trial 15525 Treatment Assignment

Subjects were sequentially assigned to a unique Subject ID number in ascending numerical order as they were screened for the study. Each subject number was randomized to a treatment sequence according to a computer generated randomization list. The treatment randomization list was computer generated by a Bayer statistician (or designated representative) and provided to the clinical study site.

Trial 15525 Analysis Sets

• Safety set: all subjects who were randomized and took at least 1 dose of the investigational product
• **Modified safety set**: all subjects who took at least 1 dose of the investigational product, who were enrolled in the Run-In Period, but who were not randomized

• **Evaluable set**: The evaluable population included all randomized subjects who provided PD serum TXB2 endpoint data at Hour 24 on Day 16 without major protocol violations. Subjects with protocol violations were identified prior to database lock. Violations might have included, but were not limited to, significant violations of inclusion/exclusion criteria, noncompliance with the investigational treatment regimen, the use of prohibited medications, and non-adherence to study protocol procedures. Subjects who did not demonstrate at least 98% serum TXB2 inhibition at predose on Day 7 or who did not provide serum TXB2 inhibition data at Hour 24 on Day 16 were excluded from the statistical analyses for the evaluable population.

**Trial 15525 Analytical Plan**

• **Primary endpoint**
  o Inhibition of serum TXB2 on Day 16 at 24 hours post IR ASA 81 mg administration in all groups

• **Secondary endpoints**
  o Inhibition of serum TXB2 on Days 7, 16, 17, and 19 of the in-house Treatment Period at 1, 3, 6, 12, 18, and 24 hours (except at 24 hours on Day 16) post IR ASA 81 mg administration in all groups  
  o Inhibition of AA-induced platelet aggregation on Days 7, 16, 17, and 19 at 1, 3, 6, 12, 18, and 24 hours post IR ASA 81 mg administration in all groups

• **Exploratory endpoints**
  o Inhibition of TXB2 using platelet-rich plasma (PRP) on Days 7, 16, 17, and 19 of the in-house Treatment Period at 1, 3, 6, 12, 18, and 24 hours post IR ASA 81 mg administration in all groups

The sponsor states the following regarding the analysis plan (FSR p 44/3119):

For the primary PD analysis, the mean and the lower bound of the corresponding one-sided 95% CI for the serum TXB2 inhibition at Hour 24 on Day 16 for each treatment group were calculated. In addition, the median and its lower bound of one-sided 95% CI, minimum, maximum, two-sided 95% CI of mean, and the number and the percentage of subjects with inhibition of serum TXB2 greater than or equal to 95% and 90% also were calculated by treatment group.

The one-sided 95% CIs for the inhibition of serum TXB2 at Hour 24 on Day 16 were examined for each group. No PD interaction was claimed if the lower bound of the one-sided 95% CI constructed for the inhibition of serum TXB2 at Hour 24 on Day 16 was greater than or equal to 95% for all treatment groups. Only the
primary endpoint was used in the assessment of a PD interaction. As the primary analysis, the evaluable population was used for the analysis of the primary endpoint. In addition, the safety population was also analyzed as sensitivity analysis.

Secondary and exploratory endpoints were analyzed similarly to the primary endpoint. Ten subjects per treatment group in the evaluable population were considered sufficient to assess the primary endpoint of inhibition of TXB2. All treatment groups did in fact have at least 10 subjects in its evaluable set.

**Trial 15525 Protocol Deviations:**

- TXB2 and platelet aggregation collected outside of window
- TXB2 re-collected due to hemolysis
- Platelet aggregation results lost due to power outage
- Platelet aggregation redrawn due to clotting, hemolysis, or laboratory request
- Platelet aggregation results not saved due to computer malfunction
- IR ASA and naproxen sodium dose administered outside of window
- Subject not attending IR ASA dose
- Predose vital sign respiration rate and pulse rate collected outside of window
- Inadvertent unblinding, about which the sponsor states the following (FSR p 49/3119):

  “The laboratory performing the serum and plasma thromboxane analysis of the blood samples was inadvertently unblinded to the group assignment and the expert advisor was partially unblinded to the group assignment. This deviation occurred because the clinical laboratory sent serum and platelet-rich plasma (PRP) samples to the laboratory for analysis of TXB2 with the sample manifest that included the group assignments. The identity of the treatment was not provided, only the subject group designation. The group designations were used by the analyst to optimize dilution of the samples to minimize the number of samples that would need to be re-assayed because they were above the quantitation limit. The analyst analyzed the samples from each respective group without dilution and then estimated appropriate dilution for each sample in each group. The use of the group designation was solely for estimating dilution factor. In addition, Northeast Bioanalytical Laboratories periodically sent blinded data for technical expert review related to the conduct and performance of the assays. On 1 occasion, the data file contained group identified information for Subjects through A corrective action was put in place. Overall, there was no impact to the study results/outcome.”

**Trial 15525 Disposition of Subjects:**

Overall, 117 subjects were enrolled into the Run-In Period, of which 15 (12.8%) were not randomized for a variety of reasons that are shown in the table below (from the FSR, p 48/3119):
However, all subjects who were randomized completed the study – all had end-of-study assessments, per the table below (FSR p 48/3119):

### Table 3: Subject Disposition in the Run-In Period (All Subjects Enrolled in Run-In Period)

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Overall n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Subjects</td>
<td></td>
</tr>
<tr>
<td>Enrolled in Run-In Period</td>
<td>117</td>
</tr>
<tr>
<td>Modified safety population</td>
<td>117</td>
</tr>
<tr>
<td>Randomized on Day 7</td>
<td>102 (87.2)</td>
</tr>
<tr>
<td>Non-randomized</td>
<td>15 (12.8)</td>
</tr>
<tr>
<td>Reason for not randomized</td>
<td></td>
</tr>
<tr>
<td>Noncompliance</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Could not verify doses on Days 2 and 3</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Positive urine drug screen on Day 6</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Investigator’s decision</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Prerandomization elimination on Day 7 - unable to collect blood</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Prerandomization elimination due to increased pulse rate on Day 7</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (8.5)</td>
</tr>
<tr>
<td>Discontinue on Day 7. Subject was excluded due to arachidonic acid level &gt;20%</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Back-up subject - prerandomization elimination on Day 7</td>
<td>8 (6.8)</td>
</tr>
</tbody>
</table>

Note: Percentages are based on the number of subjects in the modified safety population. Data source: Table 14.1.1.1

### Table 4: Subject Disposition in the Treatment Period (Safety Population)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Disposition</th>
<th>Group 1 N=17 n (%)</th>
<th>Group 2 N=17 n (%)</th>
<th>Group 3 N=17 n (%)</th>
<th>Group 4 N=17 n (%)</th>
<th>Group 5 N=17 n (%)</th>
<th>Group 6 N=17 n (%)</th>
<th>Overall N=102 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects completed</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>102 (100)</td>
<td></td>
</tr>
<tr>
<td>Subjects discontinued</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Percentages are based on the number of subjects in the safety population in each treatment group and overall.

* Group 1 = Naproxen sodium (NapSo) 220 mg administered at the same time as immediate release aspirin (IR ASA) 81 mg
  
  Group 2 = NapSo 220 mg administered 30 minutes before IR ASA 81 mg
  
  Group 3 = NapSo 220 mg administered 8 hours before IR ASA 81 mg
  
  Group 4 = IR ASA 81 mg administered alone
  
  Group 5 = IR ASA 81 mg administered 30 minutes before NapSo 220 mg
  
  Group 6 = NapSo 220 mg administered 30 minutes before IR ASA, followed by second dose of NapSo 220 mg administered 12 hours after first NapSo dose

Data source: Table 14.1.1.2
For the evaluable population, twenty-two subjects were excluded because the subjects did not demonstrate at least 98% serum TXB2 inhibition at predose on Day 7, as shown in the table below (FSR p 50/3119):

### Table 5: Summary of Populations in the Treatment Period

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Safety population</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>17 (100)</td>
<td>102 (100)</td>
</tr>
<tr>
<td>Evaluable population</td>
<td>13 (76.5)</td>
<td>14 (82.4)</td>
<td>15 (88.2)</td>
<td>13 (76.5)</td>
<td>10 (58.8)</td>
<td>15 (88.2)</td>
<td>80 (78.4%)</td>
</tr>
</tbody>
</table>

Note: Percentages are based on the number of subjects in the safety population in each treatment group and overall.

- **Group 1** = Naproxen sodium (NapSo) 220 mg administered at the same time as immediate release aspirin (IR ASA) 81 mg
- **Group 2** = NapSo 220 mg administered 30 minutes before IR ASA 81 mg
- **Group 3** = NapSo 220 mg administered 8 hours before IR ASA 81 mg
- **Group 4** = IR ASA 81 mg administered alone
- **Group 5** = IR ASA 81 mg administered 30 minutes before NapSo 220 mg
- **Group 6** = NapSo 220 mg administered 30 minutes before IR ASA, followed by second dose of NapSo 220 mg administered 12 hours after first NapSo dose

The safety population included all subjects who were randomized and took at least 1 dose of investigational product.

The evaluable population included all randomized subjects who provided serum TXB2 endpoint at Hour 24 on Day 16 without major protocol violations.

Data source: Table 14.1.1.2

**Trial 15525 Demographics (FSR p 51/3119)**

Overall, the mean age of the enrolled subjects was 37.1 years, roughly 1/3 were female, and approximately 25% Black or African American, per the table below (FSR p 51/3119):
From the evaluable analysis set, interference by NAP with the antiplatelet effect of low dose ASA was present in all NAP-ASA combination treatment groups, regardless of the timing of the administration of the two drugs, as demonstrated by the lower bound of one-sided 95% CI of the mean of serum TXB2 inhibition at Hour 24 postdose on Day 16 decreasing to a value of less than 95%, as seen in the following figure (FSR p 57/3119):

Trial 15525 Primary Analysis (FSR p 51/3119)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Non-Randomized</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 17</td>
<td>N = 17</td>
<td>N = 17</td>
<td>N = 17</td>
<td>N = 17</td>
<td>N = 17</td>
<td>N = 15</td>
<td>N = 117</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>41.3(8.46)</td>
<td>31.2(7.19)</td>
<td>37.5(13.41)</td>
<td>34.2(8.76)</td>
<td>38.8(12.09)</td>
<td>38.9(13.74)</td>
<td>38.2(11.00)</td>
<td>37.1(10.00)</td>
</tr>
<tr>
<td>Median</td>
<td>40.0</td>
<td>30.0</td>
<td>34.0</td>
<td>31.0</td>
<td>34.0</td>
<td>38.0</td>
<td>36.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Range</td>
<td>30.61</td>
<td>21.45</td>
<td>20.64</td>
<td>24.53</td>
<td>22.64</td>
<td>23.67</td>
<td>18.61</td>
<td>18.67</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7(41.2%)</td>
<td>4(23.5%)</td>
<td>6(35.3%)</td>
<td>4(23.5%)</td>
<td>4(23.5%)</td>
<td>7(41.2%)</td>
<td>4(26.7%)</td>
<td>36(30.8%)</td>
</tr>
<tr>
<td>Male</td>
<td>10(58.8%)</td>
<td>13(76.5%)</td>
<td>11(64.7%)</td>
<td>13(76.5%)</td>
<td>11(64.7%)</td>
<td>11(58.8%)</td>
<td>11(73.3%)</td>
<td>81(69.2%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>11(64.7%)</td>
<td>14(82.4%)</td>
<td>11(64.7%)</td>
<td>12(70.6%)</td>
<td>11(64.7%)</td>
<td>12(80.0%)</td>
<td>82(70.1%)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>6(35.3%)</td>
<td>2(11.8%)</td>
<td>6(35.3%)</td>
<td>4(23.5%)</td>
<td>4(23.5%)</td>
<td>4(23.5%)</td>
<td>29(24.8%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>1(5.9%)</td>
<td>0</td>
<td>1(5.9%)</td>
<td>0</td>
<td>3(2.6%)</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native Hawaiian or Other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2(1.7)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>7(41.2%)</td>
<td>9(52.9%)</td>
<td>4(23.5%)</td>
<td>6(35.3%)</td>
<td>7(41.2%)</td>
<td>5(29.4%)</td>
<td>3(20.0%)</td>
<td>41(35.0%)</td>
</tr>
<tr>
<td>Non-Hispanic/Non-Latino</td>
<td>10(58.8%)</td>
<td>8(47.1%)</td>
<td>13(76.5%)</td>
<td>11(64.7%)</td>
<td>10(58.8%)</td>
<td>12(70.6%)</td>
<td>76(65.0%)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>78.20(12.537)</td>
<td>73.16(13.266)</td>
<td>72.82(9.501)</td>
<td>73.28(9.914)</td>
<td>79.89(16.347)</td>
<td>73.45(9.520)</td>
<td>78.27(12.851)</td>
<td>75.54(12.220)</td>
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<tr>
<td>Median</td>
<td>77.00</td>
<td>79.20</td>
<td>71.80</td>
<td>74.00</td>
<td>79.10</td>
<td>73.20</td>
<td>80.50</td>
<td>75.20</td>
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<tr>
<td>Range</td>
<td>53.1</td>
<td>51.2</td>
<td>50.5</td>
<td>57.1</td>
<td>55.4</td>
<td>60.1</td>
<td>56.7</td>
<td>50.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>170.12(11.095)</td>
<td>169.44(9.103)</td>
<td>169.75(11.126)</td>
<td>174.51(5.231)</td>
<td>173.75(11.208)</td>
<td>167.80(7.007)</td>
<td>173.78(7.007)</td>
<td>171.27(9.849)</td>
</tr>
<tr>
<td>Median</td>
<td>170.60</td>
<td>171.00</td>
<td>169.80</td>
<td>175.90</td>
<td>172.60</td>
<td>172.00</td>
<td>172.60</td>
<td>172.40</td>
</tr>
<tr>
<td>Range</td>
<td>148.0</td>
<td>149.8</td>
<td>148.8</td>
<td>164.0</td>
<td>149.2</td>
<td>153.1</td>
<td>153.6</td>
<td>148.0</td>
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<tr>
<td>BMI (kg/m²)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>26.86(2.133)</td>
<td>25.29(3.007)</td>
<td>25.31(2.802)</td>
<td>24.06(3.130)</td>
<td>26.25(3.283)</td>
<td>26.00(3.116)</td>
<td>25.86(3.024)</td>
<td>25.66(2.865)</td>
</tr>
<tr>
<td>Median</td>
<td>27.50</td>
<td>26.00</td>
<td>24.80</td>
<td>23.60</td>
<td>27.60</td>
<td>26.00</td>
<td>26.90</td>
<td>26.00</td>
</tr>
<tr>
<td>Range</td>
<td>22.4</td>
<td>19.7</td>
<td>19.9</td>
<td>18.9</td>
<td>19.6</td>
<td>21.3</td>
<td>20.9</td>
<td>18.9</td>
</tr>
</tbody>
</table>
A sensitivity analysis of the safety population demonstrated essentially the identical results, though most of the results from that analysis were numerically worse (from comparison of FSR data tables 14.2.1.1 and 14.2.1.2, not shown).

**Trial 15525 Prespecified TXB2 Inhibition Secondary Analyses – Serum**

As convincing as the primary analysis was, the striking result from trial 15525 was demonstrated in NAP Run-Out Period, days 17-19, during which low dose ASA was continued and NAP stopped. The interaction was prominent in all treatment groups of the Evaluable Set, as is shown in the following sequence of PD assessments of serum TXB2 inhibition with respect to time for each of the six treatment arms (FSR pp 59-64):
Figure 3: Serum TXB\textsubscript{2} Inhibition (%) – Mean and One-Sided 95% CI by Time Point for Each Group (Evaluable Population)

Group 1: Naproxen sodium 220 mg administered at the same time as immediate release aspirin 81 mg

Figure 4: Serum TXB\textsubscript{2} Inhibition (%) – Mean and One-Sided 95% CI by Time Point for Each Group (Evaluable Population)

Group 2: Naproxen sodium 220 mg administered 30 minutes before immediate release aspirin 81 mg
Figure 5: Serum TXB₂ Inhibition (%) – Mean and One-Sided 95% CI by Time Point for Each Group (Evaluable Population)

Group 3: Naproxen sodium 220 mg administered 8 hours before immediate release aspirin 81 mg

Figure 6: Serum TXB₂ Inhibition (%) – Mean and One-Sided 95% CI by Time Point for Each Group (Evaluable Population)

Group 4: Immediate release aspirin 81 mg administered alone
Figure 7: Serum TXB2 Inhibition (%) – Mean and One-Sided 95% CI by Time Point for Each Group (Evaluable Population)

Group 5: Immediate release aspirin 81 mg administered 30 minutes before naproxen sodium 220 mg

Figure 8: Serum TXB2 Inhibition (%) – Mean and One-Sided 95% CI by Time Point for Each Group (Evaluable Population)

Group 6: Naproxen sodium 220 mg administered 30 minutes before immediate release aspirin, followed by second dose of naproxen sodium 220 mg administered 12 hours after first naproxen sodium dose.
The sponsor obtained similar results for the sensitivity analyses of these secondary TXB2 analyses using the safety set though the numerical nadirs of TXB2 inhibition were generally lower for the safety set.

**Trial 15525 Prespecified TXB2 Inhibition Exploratory Analyses – Plasma**

The overall trends in the demonstration of the NAP-ASA interaction were also demonstrated in the plasma analyses of the evaluable population, though the magnitudes of the interactions in the various combination treatment groups were numerically higher (worse) in the plasma analyses of these treatment groups, as compared to the above serum analyses. The sequence of PD assessments of serum TXB2 inhibition with respect to time for each of the six treatment arms as shown below (FSR pp 252-257 of 3119):
Trial 15525 Prespecified AA-induced Platelet Aggregation Inhibition Secondary Analyses – Evaluable Population

As might be expected from a functional assay, there was more variability in the AA-induced platelet aggregation results between, both between the groups at the end of the run-in (day 7 predose), on day 16 @ 24 hours, and at the time coinciding with the TXB2 inhibition nadirs in serum and plasma (day 17 @ 24 hours post ASA, and day 17 @ 18 hours post ASA, respectively). Because of this variability, the sponsor assessed median values for aggregation inhibition preferentially. AA-induced aggregation inhibition at
these four time points for the evaluable population are shown in the following four sponsor tables (FSR pp 145, 157, 162,
About these results, the sponsor noted the following:

- A broad range of baseline AA-induced platelet aggregation scores
- Considerable variability and extreme values in the post-baseline inhibition results
- Generally lower inhibition of AA-induced platelet aggregation across all time points on day 16 hour 24 when naproxen sodium 220 mg was administered with IR ASA 81 mg, compared with IR ASA 81 mg administered alone
- Only Group 4 (IR ASA alone) produced a median value above 90% at all Day 16 observations
- During the run-out, only Group 4 (IR ASA alone) consistently produced a median value above 90% (except Day 17 Hour 1; 89.47%)

DCRP would add to these sponsor observations that extremely low values for percent inhibition of AA-induced platelet aggregation (lower 95% CI of the median result) are all isolated to the NAP treatment arms. We think it would be useful for the sponsor to create figures of inhibition of AA-induced platelet aggregation as a function of time (as was done to create the figures for TXB2 inhibition), so that platelet aggregometry in the various NAP treatment groups can be visually assessed with respect to its behavior during the washout.

**Assessments**

1. **Data quality.** While trial 15525 was not perfectly executed (see Trial 15525 Protocol Deviations, page 21 of this review), I agree with the sponsor that most of the errors that occurred did not impact the overall results of this important trial, which was robustly designed to answer the following agency questions:

   - Is there an interaction between NAP and ASA?
   - If so, what is the timing of the development of the interaction, and how does the interaction behave during NAP washout that would recapitulate what
occurs when low dose NAP is started and then stopped in the OTC setting for symptoms that come and go?

- If so, does dosing ASA before NAP resolve the interaction?
- If so, how many hours after the administration of NAP can ASA be taken without losing its cardio-protective effects?

Probably one of the most important design elements of trial 15525 was to remove the confounding effects of ASA non-compliance during an unobserved ASA run-in. Poor compliance during this period causes a low baseline inhibition of the PD parameters of interest that then appear to improve (sometimes dramatically) as the more rigorously performed treatment periods of these types of trials ensue. The resulting increases in TXB2 inhibition and platelet aggregation inhibition results due to compliance effects (which often get labeled “aspirin resistance”) can overwhelm the negative interaction between the drugs, thereby sabotaging an interaction trial’s resolving power to show the effect of interest. Aspirin compliance during the run-in of this trial was reasonably aggressively assured by protocol driven supervision of the run-in.

2. Trial results. Corroborating our suspicions from the work of Anzellotti et al (2011), the interaction between NAP and ASA is reproducibly seen in all NAP-ASA combination treatment groups in trial 15525. The trial’s findings are remarkably internally consistent. While the interaction seems to be of a lesser magnitude when ASA is dosed 30 minutes before NAP, it is not abolished. In the circumstance of the amplified signaling systems involved in platelet activation, it is not clear that a lessor magnitude of NAP-ASA interaction measured by these PD parameters translates into fewer CV events that may result.

3. Clinical implications. There are no RCT CV outcomes data assessing this interaction. However, it would be reasonable to expect that there will be a continuum of risk for CV outcome consequences of this interaction based on the background severity of the underlying cardiovascular disease, the most extreme risk groups involving those having recently experienced a CV event, those having recently undergone coronary artery bypass grafting, or those taking DAPT for a recent stent implant post ACS.

4. Implications for other formulations. Trial 15525 tested 81 mg of IR ASA and naproxen sodium, 220 mg qd. From a clinical standpoint, we would expect the interaction demonstrated in trial 15525 may:

- Be more prominent with enteric coated ASA (EC-ASA) due to the lower Cmax of the enteric coated aspirin product. The delayed absorption of enteric coated aspirin could also make the interaction more prominent if NAP were given close to the same time as EC-ASA.

- Occur with higher (prescription) doses of NAP after their discontinuation, given that the suspected mechanism of the interaction is reversible binding of NAP that competes with and prevents aspirin-mediated acetylation of platelet SER529.
From the Group 6 (NAP 220 mg BID) data in trial 15525, in which the NAP-ASA interaction during the run-out was one of the most prominent of all the experimental treatment groups tested, we would expect that higher and more frequent dosing of NAP might avert the development of platelet reactivity during therapy, but that the NAP-ASA interaction would still occur during NAP washout, albeit later after discontinuation than was seen with the lower NAP dose used in trial 15525.

5. **Implications for labeling.** Unless a sponsor reproduces trial 15525 using EC-ASA with their NAP formulation and demonstrates no interaction during treatment and during the run-out (the latter extended appropriately for the EC-ASA product), it must be assumed that this interaction will occur, and all NAP products should be labeled so that patients taking any formulation of low-dose ASA for CV event prophylaxis (neurological or cardiac) will be made aware that other NSAID choices may carry less risk for them developing drug-interaction-related CV events. While this is true for those taking ASA for primary prevention, we think it is particularly relevant for those taking ASA for secondary prevention, especially those who have had recent CV events and/or CV interventional procedures.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRESTON M DUNNMON
09/05/2016

MARTIN ROSE
09/05/2016

NORMAN L STOCKBRIDGE
09/06/2016
Date: March 16, 2018
Reviewer(s): Chih-Ying Pratt, Ph.D.
Division of Epidemiology II
Team Leader: Monique Falconer, M.D., M.S.
Division of Epidemiology II
Division Director: Lockwood Taylor, Ph.D., M.P.H
Division of Epidemiology II
Subject: Literature review update: epidemiology studies on thrombotic cardiovascular events related with nonsteroidal anti-inflammatory drugs use
Drug Name(s): Celebrex (celecoxib) and other nonsteroidal anti-inflammatory drugs (NSAIDs)
Application Type/Number: NDA 20998
Applicant/sponsor: Pfizer
OSE RCM #: 2017-1906
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Attachment I: DEPI Director memo
Attachment II: NASID class labeling on the risk of thrombotic cardiovascular events (using Celebrex label as an example)
1. BACKGROUND

In February 2005, FDA’s Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) convened a joint advisory committee meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) on the emergent data about the risk of cardiovascular (CV) thromboembolic events associated with the cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAID), rofecoxib and celecoxib. During the 2005 meeting, data from clinical trials and epidemiology studies of individual NSAIDs were reviewed, and the committee discussed the risk of CV thromboembolic events associated with the use of COX-2 selective and nonselective NSAIDs (traditional NSAIDs [tNSAID]). Based on the data reviewed and the deliberations of the advisory committee members, FDA concluded that the risk for CV thromboembolic events was present for COX-2 selective NSAIDs and tNSAIDs, and the available data did not permit ranking the drugs with respect to CV risk.\(^a\)

In April 2005, the FDA asked all the Sponsors of marketed prescription NSAIDs to revise the label for their products to include a boxed warning highlighting the potential for increased risk of CV events and the well-described serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. In addition, the Celebrex labeling also contains safety data from long-term treatment trials with celecoxib. FDA also requested that the manufacturers of non-prescription (over-the-counter) NSAIDs revise their monograph to provide more specific information about the potential CV and GI risks of their individual products and remind patients of the limited dose and duration of treatment of these products in accordance with the package instructions.\(^b\)

Around the time of the 2005 labeling approval, the FDA requested that Pfizer conduct a randomized controlled trial to study the cardiovascular risk of celecoxib compared to ibuprofen and naproxen. That study was entitled, Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION).

In May 2011, a new study was published using the Danish National Registry study\(^1\) that described an early risk of CV events in post-MI patients taking NSAIDs. DAAAP decided to review the substantial literature on cardiovascular risk with NSAIDs that had been published since the labeling change in 2005. The Division of Epidemiology (DEPI) was consulted to collaborate on this review. During literature review, DAAAP learned of a large meta-analysis of randomized clinical trials that was being conducted by the Coxib and Traditional NSAID Trialists’ (CNT) Collaboration based at Oxford University under the direction of Professor Colin Baigent.\(^2\) The meta-analysis supported the 2005 conclusions that there is a risk for CV events for both tNSAIDs and COX-2 selective NSAIDs. However, the meta-analysis also raised the possibility that, in contrast to the 2005 conclusions, there may be a lower risk for one tNSAID, naproxen. Based on


\(^{b}\) https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm429364.htm
the literature review of 90 epidemiology publications and the CNT meta-analysis, the DEPI reviewer, Dr. Andrew Mosholder, concluded that there was sufficient evidence that among tNSAIDs, naproxen was likely to have less cardiovascular risk than other tNSAIDs, particularly for myocardial infarction (MI).

In February 2014, a second joint advisory committee meeting of the AAC and DSaRM was held to discuss updating the NSAID label based on the observational and clinical trial data published since the 2005 label changes. Dr. Mosholder presented the results of his review and his DEPI-supported recommendation to label naproxen as having a lower risk than the other tNSAIDs. During the Open Public Hearing and committee members’ discussions at the 2014 advisory committee meeting, concerns were raised regarding the CNT and the observational studies that supported a differential CV risk between individual NSAIDs. Mainly, there were no direct comparisons between agents, and the studies did not adequately control for differences in NSAID dose or the severity of the underlying disease indicating NSAID therapy.

The committee members determined that while these findings suggested that naproxen may have a lower risk, they did not provide sufficient evidence to support a label change. The committee also concluded that the long-term clinical outcome trial, PRECISION, could provide additional data describing the CV risk associated with celecoxib, as the trial would evaluate the relative safety of celecoxib and naproxen and ibuprofen.

DEPI leadership considered discussions around the level of uncertainty with these findings, and after further discussions with DAAAP, aligned with DAAAP on the need for more certainty around these data prior to adding language to labeling suggesting that naproxen has a safer cardiovascular profile. For there to be more certainty, studies with “head-to-head” comparisons between naproxen and other NSAIDs (both tNSAIDs and celecoxib) that are adequately powered and able to adjust for differences in severity of underlying illness as well as in NSAID dose would be needed (See Appendix I: DEPI Director memo by Dr. Judy Staffa).

A Drug Safety Communication (DSC) was issued in July 2015. Without singling out naproxen, the DSC alerted the prescribing community that there may be differences in cardiovascular risk between NSAIDs. The DSC also notified the prescribing community that the Boxed Warning and Warnings and Precautions sections of NSAID class labeling would be revised to reflect the additional findings since the original labeling was approved in 2005. The NSAID class label revised in 2016 also addressed time to event, vulnerable populations and risk factors regarding the CV thrombotic event risk associated with NSAIDs (See Appendix II: current NSAIDs class

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c Complete safety reviews, background information, and minutes of this advisory committee meeting are available at http://wayback.archive-it.org/7993/20161022142708/ http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm380883.htm
d We note that despite committee conclusions as well as several internal FDA post-advisory committee discussions, Dr. Mosholder did not change his recommendation to label naproxen as having a lower risk than the other tNSAIDs. Thus, DEPI leadership issued a Director’s dissent memo to document differences in the positions of Dr. Mosholder and DEPI leadership.
warning on thrombotic CV events).

The results of PRECISION were published in the New England Journal of Medicine in November 2016, and the Sponsor submitted the clinical study report to DAAAP for review in June 2017. Another joint advisory committee meeting is scheduled for April 2018 to discuss the findings of PRECISION. In preparation for advisory committee meeting, DAAAP consulted DEPI to conduct a review of the epidemiological studies published since the last review was completed in 2013. DAAAP requested that only studies that advance the current understanding of the risk of CV thrombotic events associated with NSAID use be included in the literature search.

2. REVIEW METHODS AND MATERIALS

DAAAP requested that DEPI-II focus the current literature review on the same questions that were the focus of the 2013 literature review:

1. Are there data to better refine the understanding of time to event for cardiovascular risk (including stroke) with NSAIDs? Early hazard versus increased risk with cumulative use (or both, depending on the population)?
2. Describe any data that suggest specific vulnerable populations (e.g., history of MI, CV risk factors, post-operative coronary artery bypass graft [CABG] or others) for NSAID-associated CV risk (including stroke)
3. Does use of NSAIDs in patients with history of MI increase the risk of recurrent MI or death?
4. Are there data to support differential CV risk (including stroke) across the specific NSAIDs?

DEPI searched the National Library of Medicine’s PubMed database on January 24, 2018. The search strategy is described in detail in the Appendix (Section 6). Using search strings for non-steroidal anti-inflammatory agents and the targeted thrombotic CV adverse outcomes, DEPI identified 2,389 English language articles published from 12/04/2012 to 1/24/2018. The exclusion criteria were:

- Publications that did not report on a research study (e.g. commentaries and reviews)
- Animal studies, cellular studies, pharmacokinetic studies, pharmacodynamics studies
- Non-observational studies (e.g. randomized control trials, case reports, case series)
- Meta-analysis, cross-sectional studies, or studies that only conducted descriptive analyses
- Studies that did not address the four target questions
- Studies that did not include thrombotic CV events as a primary outcome
- Studies that were included in previous DEPI review or that used the same data as the publications included in previous review
DEPI identified 12 potential observational studies that evaluated the risk of CV thrombotic events associated with NSAID use.\(^3\)-\(^{14}\) DEPI further evaluated the quality of these studies based on whether their findings could be used to support additional labeling changes with regard to a differential CV risk between NSAIDs, vulnerable populations, risk factors, or time to event.

3. LITERATURE SEARCH RESULTS

The 12 publications included four cohort studies,\(^{8,11-13}\) six case-control studies\(^{3,5-7,9,14}\) and three self-controlled studies\(^{4,10,13}\) conducted in eight non-U.S. countries\(^e\) that met the PubMed search criteria. Eight studies were based on administrative claims data from nationwide health insurance plans,\(^3,5,7,8,10,11,13\) one was based on prospectively collected patient registry data,\(^{12}\) and three were based on a primary healthcare provider database.\(^6,9,14\)

4. DISCUSSION

Differential CV risk between NSAID products

To support labeling recommendations regarding a differential CV risk between NSAID products, DEPI looked for evidence from “head-to-head comparisons between NSAIDs that were adequately powered and able to adjust for differences in severity of underlying illness as well as in NSAID dose.” –a criterion in Dr. Staffa’s memo (Appendix I).

Among the 12 identified studies, 11\(^f\) attempted to address whether a differential CV risk exists between NSAID products.\(^3,5-14\) The evaluation of the 11 studies based on the DEPI’s criterion is summarized below and in Table 1:

- Nine of the 11 identified studies that examined CV risk by NSAID products used “non-users” or “non-current users” as comparators,\(^3,5-9,11,13,14\) and only one of the nine studies accounted for NSAID dose in the analyses.\(^3\) Confounding by the severity of NSAID indication or NSAID dose, or both, remain a concern for the nine studies.

- Two studies used a self-controlled design,\(^{10,13}\) and one study, conducted in a population of patients with osteoarthritis or rheumatoid arthritis, compared patients who were prescribed celecoxib to patients prescribed “all other (non-celecoxib) NSAIDs”.\(^{12}\) While using patients as their own comparison and the restriction to treated patients with same indication for NSAIDs both could reduce the concern of confounding by NSAID indications, the three studies did not adjust for NSAID dose. Thus, confounding by NSAID dose is still a concern.

- None of the studies reported \textit{a priori} calculations to support sufficient power to derive precise effect estimates for any of the studied NSAIDs.

Therefore, DEPI determined that none of these studies can provide quality data to inform whether there is differential CV risk across NSAIDs.

\(^e\) Denmark (N=3), Taiwan (N=3), Spain (N=2), Germany, Japan, Korea, United Kingdom, Canada.

\(^f\) One of the 11 studies (by Fosbol et al.) approached the research question with two study designs: a cohort design (with non-user comparator) and a self-control design.
Table 1. Summary of design issues of the identified studies reported CV risks by NSAIDs

<table>
<thead>
<tr>
<th>Reference; Author</th>
<th>Study design</th>
<th>Reference group</th>
<th>Accounted/adjusted for the severity of NSAID indication</th>
<th>Accounted/adjusted for NSAID dose</th>
<th>Report a priori power calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>#3 Bally et al., 2018</td>
<td>Nested case-control</td>
<td>Non-use of studied NSAIDs</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>#5 Thone et al., 2017</td>
<td>Nested case-control</td>
<td>Past use of studied NSAIDs (≥ 184 days prior to the index date)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#6 Dalal et al., 2017</td>
<td>Nested case-control</td>
<td>Remote use of studied NSAIDs (between 60 days and 1 year prior to index date)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#7 Wu et al., 2016</td>
<td>Case-control</td>
<td>Non-use of studied NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#8 Kim et al., 2015</td>
<td>Cohort</td>
<td>Non-users of studied NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#9 Garcia-Poza et al., 2015</td>
<td>Case-control</td>
<td>Non-use of NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#10 Chuang et al., 2015</td>
<td>Case-crossover</td>
<td>Self-control</td>
<td>Maybe (by using individual patients as their own control)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#11 Lindhardsen et al., 2014</td>
<td>Cohort</td>
<td>Non-users of studied NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#12 Hirayama et al., 2014</td>
<td>Cohort</td>
<td>Users of other (i.e. non-celecoxib) studied NSAIDs</td>
<td>Maybe (by restricting to OA/RA patients who were treated with NSAIDs)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#13 Fosbol et al., 2014</td>
<td>Cohort</td>
<td>Non-users of studied NSAIDs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#13 Fosbol et al., 2015</td>
<td>Case-crossover</td>
<td>Self-control</td>
<td>Maybe (by using individual patients as their own control)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>#14 De Abajo et al., 2014</td>
<td>Case-control</td>
<td>Non-use of studied NSAID</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Vulnerable population or risk factors

DEPI identified one study of NSAIDs and CV risk in a vulnerable population. A case-crossover study reported that NSAID use during acute respiratory infection (ARI) episodes is associated with higher increased risk of MI, compared to NSAID use alone, or having ARI episode without NSAID use (relative to no exposure to NSAIDs or ARI). However, the study was based on claims data, which are unable to capture the severity of ARI. NSAIDs might have been prescribed to patients who have more severe ARI. Given that ARI is also a risk factor for MI, the higher observed risk among NSAID use during ARI episodes could be due to the confounding by ARI severity.

Consequently, DEPI does not recommend changing the label language on vulnerable populations or risk factors based on this one study.

Time to event of NSAID associated CV risk

The current NSAID class label carries the warning that the increased risk of serious CV thrombotic events can begin as early as the first weeks of NSAID treatment, based on observational studies identified in DEPI’s previous literature review and recommendations from the 2014 advisory committees. It is less clear if the risk would increase by the length of NSAID treatment. From the current literature search, DEPI identified one nested case-control study that explored the temporal relationship between NSAID exposure and acute MI risk. The study was the first to use an advanced analytical method (i.e. the Weighted Cumulative Exposure, WCE) to simultaneously account for dose and timing of past exposure when characterizing NSAID-associated CV risk. The findings confirmed that current, and very recent exposure of all NSAIDs had the greatest impact on MI risk. The authors speculated some NSAIDs might be safer than others, given that the duration of the exposure prior to a statistically significant increased MI risk varied among the NSAIDs. Despite some strengths of this approach, the reference group in the study was “non-users” and no formal statistical tests were performed comparing the NSAIDs head-to-head. DEPI disagrees that the study provided evidence that an increased CV risk is different between NSAIDs, based on duration or exposure prior to an event. Furthermore, while the study modeled the association between NSAIDs and MI risk up to 90 days of exposure, it did not characterize NSAID-related CV risk beyond 90 days of exposure.

Therefore, DEPI does not recommend changing the label regarding the time to event of NSAID-associated CV thrombotic event.

5. CONCLUSION

The observational studies published after the DEPI literature review completed in 2013 do not advance our current knowledge on thrombotic CV event risk associated with NSAID use. They do not meet the criteria laid out in the 2015 DEPI Director memo — using “head-to-head” comparisons among NSAIDs, adequately powered and able to adjust for differences in severity of underlying illness as well as in NSAID dose. Therefore, DEPI does not recommend

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8 [https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm](https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm)
additional labeling changes regarding a differential CV risk between products, vulnerable populations, risk factors, or time to event based on the observational studies published since the DEPI literature review completed in 2013.
6. REFERENCES


APPENDIX

SEARCH STRATEGY AND SEARCH TERMS
Search and screening process of identifying articles for in-depth review (Steps and number of articles left)

1. Search “NSAID” in title, abstract or Medical Subject Headings (MeSH”), identified 220372 articles
2. Search “targeted CV adverse events” in title, abstract or MeSH”, identified 669985 articles
3. Combined step #1 and #2 220372
4. Restrict to English Article and desired time frame (12/04/2012 to 12/24/2018) 2389
5. Exclude animal, cellular, pharmacokinetic/pharmacodynamics studies 1715
6. Required key words of “observational study” 818
7. Excluded wrong publication or study type in title or abstract 503
8. Excluded 491 articles after reviewer screening
   - 455 studies that did not address the four focused questions
   - 12 studies that did not include thrombotic CV events as a primary outcome
   - 21 meta-analysis, cross-sectional studies, or studies that only conducted descriptive analyses
   - 3 studies that were included in previous DEPI review or used the same data as the publications that was included in previous review

→12 articles reported observational data on the 4 target questions
Search terms

- **NSAID**

- **Targeted CV adverse events**

- **Animal study**

- Cellular study

- Pharmacokinetics/Pharmacodynamics studies
  pharmacokinetics[tiab] OR pharmacokinetic[tiab] OR pharmacodynamic[tiab] OR pharmacodynamics[tiab])

- Observational study key words

- Excluded study type or publication type
OR “animals”[MeSH Terms:noexp]
ATTACHMENTS

Attachment I: DEPI Director memo
Date: June 23, 2015
To: Sharon Hertz, M.D., Acting Director, Division of Anesthesia, Analgesia and Addiction Products, OND
From: Judy Staffa, Ph.D., R.Ph., Director, Division of Epidemiology II, OSE
Subject: Concurrence with regulatory actions relating to cardiovascular thrombotic events associated with NSAIDs

Drug Name(s): Nonsteroidal anti-inflammatory drugs (NSAIDs)
OSE RCM #: RCM 2011-45

The purpose of this memo is to document alignment between DEPI-II and DAAAP on language for class labeling changes for regarding risk of cardiovascular events in relation to the use of NSAIDs.

Based on reviews of 90 epidemiology publications, Dr. Andrew Mosholder (then of DEPI-II) stated that there seems to be a sufficient amount of evidence to conclude that among tNSAIDs, naproxen is likely to have a lesser cardiovascular risk and diclofenac a higher risk, particularly for MI. After his review of the CNT meta-analysis of clinical trial data, Dr. Mosholder changed his recommendation regarding diclofenac, as the trial data demonstrated that lower doses of diclofenac appeared to share similar risk to higher doses of ibuprofen, and thus did not appear to have higher risk than all other NSAIDs, as it had originally appeared in the epidemiologic data. However, Dr. Mosholder and DEPI-II continued to recommend that naproxen be labeled as having lower cardiovascular risk than other NSAIDs, based on the results of both epidemiologic studies and the CNT meta-analysis, which appeared consistent in these findings.

On February 10-11, 2014, FDA convened an advisory committee to discuss updating NSAID labeling based on observational and clinical trial data that have accumulated since class labeling was enacted in 2005. Dr. Mosholder presented the results of his review, including his DEPI-II supported recommendation to label naproxen as having a lower risk than the other tNSAIDs. This recommendation, again, was based on the consistency of findings across multiple observational studies, as well as the apparent support of this finding in the CNT meta-analysis of clinical trials.

During the Open Public Hearing part of the advisory committee meeting, Dr. Milton Packer presented his opinion about the scientific validity of the methods used by CNT to quantify the risk of CV outcomes associated with tNSAIDs (including naproxen). This method is referred to as “indirect”, since instead of comparing tNSAIDs directly with placebo (data not available), it relies on inferring that risk based on the observed risk seen when comparing tNSAIDs with coxibs, and then comparing coxibs with placebo, since those data are available. However, Dr. Packer pointed out what could be a major flaw in these analyses, since the coxib with which each tNSAID was compared in these indirect analyses was not the same; sometimes it was rofecoxib and other times it was celecoxib. Since rofecoxib and celecoxib have been shown to have a different
cardiovascular risk profile, results obtained from these comparisons could differ, based solely on the comparator group chosen. This can introduce bias into the comparisons; since naproxen was only compared with rofecoxib, which has a higher risk, it could appear to be safer than other tNSAIDs compared with celecoxib. This information introduced a level of uncertainty into the interpretation of the CNT findings.

That left the observational studies as the strongest evidence available to support naproxen having lower CV risk than other tNSAIDs. The committee further discussed the uncertainty associated with those studies, given that there were no direct comparisons between agents that were able to adequately control for differences in dose of NSAID and severity of the underlying disease indicating NSAID therapy. Their conclusion was that although these findings appear consistent and suggestive that naproxen may have a lower risk, they do not necessarily rise to the level of evidence needed to trigger a label change, but suggested that these data could indeed affect their own prescribing practices for individual patients.

Although these committee discussions, and several post-committee internal discussions, did not affect Dr. Mosholder’s recommendations to add language to NSAID class labeling about naproxen’s apparent safer risk profile, DEPI-II is now uncomfortable with the level of uncertainty around these findings, largely based upon Dr. Packer’s presentation and the committee discussion. Given the possible widespread implications for prescribing practices, and possible unintended consequence of large shifts in prescribing toward naproxen, DEPI-II can no longer support Dr. Mosholder’s labeling recommendations, and would prefer to have more certainty around these data prior to adding language to labeling suggesting that naproxen has a safer cardiovascular profile. The certainty needed relates to the need for more “head-to-head” comparisons between naproxen and other NSAIDs (both tNSAIDs and celecoxib) that are adequately powered and able to adjust for differences in severity of underlying illness as well as in NSAID dose.

In discussions between DEPI-II and DAAAP, DAAAP suggested labeling language that would alert the prescribing community that there may be differences in cardiovascular risk between NSAIDs, without singling out naproxen. DEPI-II can align with this language, because it updates the previous language which stated that all NSAIDs carry cardiovascular risk, implying that the risk is uniform, which current data suggest is not the case. There is clearly a need for more targeted research into this safety question, and DEPI-II has suggested that DEPI-II and DAAAP partner in authoring a perspective article in a widely read medical journal to explain the remaining uncertainty in these data, and to call for more studies to address these important questions. The two divisions are working together to author such an article.

The PRECISION trial, which is hoped to better inform this issue by randomizing patients to celecoxib, naproxen and ibuprofen and comparing their adverse event profiles, has completed patient recruitment and the data are now being analyzed. Once the data from this trial are submitted to the Agency for review, DEPI-II recommends updating its literature review to capture any new observational studies as well, to determine whether any new information is available that should be added to labeling. DAAAP has indicated its agreement with this path forward.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUDY A STAFFA
06/23/2015
Attachment II: NSAID class labeling on the risk of thrombotic cardiovascular events (using Celebrex label as an example)

BOXED WARNING on RISK OF SERIOUS CARDIOVASCULAR EVENTS
See full prescribing information for complete boxed warning.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. (5.1)
- CELEBREX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)

5. WARNINGS AND PRECAUTIONS
5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

In the APC (Adenoma Prevention with Celecoxib) trial, the hazard ratio for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for CELEBREX 400 mg twice daily and 2.8 (95% CI 1.1 – 7.2) with CELEBREX 200 mg twice daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction [see Clinical Studies (14.6)]. To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an
NSAID, such as celecoxib, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)].

Status Post Coronary Artery Bypass Graft (CABG) Surgery
Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of Celebrex in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If Celebrex is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.
**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**

*See full prescribing information for complete boxed warning.*

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. (5.1)
- **CELEBREX** is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)

**RECENT MAJOR CHANGES**

Boxed Warning 5/2016

Warnings and Precautions, Cardiovascular Thrombotic Events (5.1) 5/2016

Warnings and Precautions, Heart Failure and Edema (5.5) 5/2016

**INDICATIONS AND USAGE**

**CELEBREX** is a nonsteroidal anti-inflammatory drug indicated for:

- Osteoarthritis (OA) (1.1)
- Rheumatoid Arthritis (RA) (1.2)
- Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Acute Pain (AP) (1.5)
- Primary Dysmenorrhea (PD) (1.6)

**DOSEAGE AND ADMINISTRATION**

- Use the lowest effective dose for shortest duration consistent with individual patient treatment goals (2.1)
- OA: 200 mg once daily or 100 mg twice daily (2.2, 14.1)
- RA: 100 to 200 mg twice daily (2.3, 14.2)
- JRA: 50 mg twice daily in patients 10-25 kg, 100 mg twice daily in patients more than 25 kg (2.4, 14.3)
- AS: 200 mg once daily single dose or 100 mg twice daily. If no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit (2.5, 14.4)
- AP and PD: 400 mg initially, followed by 200 mg dose if needed on first day. On subsequent days, 200 mg twice daily as needed (2.6, 14.5)

Hepatic Impairment: Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B). (2.7, 8.6, 12.3)

Poor Metabolizers of CYP2C9 Substrates: Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers. (2.7, 8.8, 12.3).

**DOSEAGE FORMS AND STRENGTHS**

**CELEBREX** (celecoxib) capsules: 50 mg, 100 mg, 200 mg and 400 mg (3)

**CONTRAINDICATIONS**

- Known hypersensitivity to celecoxib, or any components of the drug product or sulfonamides (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

**WARNINGS AND PRECAUTIONS**

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- Heart Failure and Edema: Avoid use of **CELEBREX** in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of **CELEBREX** in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: **CELEBREX** is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue **CELEBREX** at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks of gestation (5.10, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

**ADVERSE REACTIONS**

Most common adverse reactions in arthritis trials (>2% and >placebo) are: abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, accidental injury, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, rash (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

**DRUG INTERACTIONS**

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRI/SNRIs): Monitor patients for bleeding who are concomitantly taking **CELEBREX** with drugs that interfere with hemostasis. Concomitant use of **CELEBREX** and analgesic doses of aspirin is not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with **CELEBREX** may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concomitant use with **CELEBREX** in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- DIuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- Digoxin: Concomitant use with **CELEBREX** can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks of gestation (5.10, 8.1)
- Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of **CELEBREX** in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 5/2016
FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events
- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction, and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. [see Warnings and Precautions (5.1)]
- CELEBREX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. [see Contraindications (4) and Warnings and Precautions (5.1)]

Gastrointestinal Bleeding, Ulceration, and Perforation
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious (GI) events. [see Warnings and Precautions (5.2)]

1. INDICATIONS AND USAGE
   CELEBREX is indicated

   1.1 Osteoarthritis (OA)
   For the management of the signs and symptoms of OA [see Clinical Studies (14.1)]

   1.2 Rheumatoid Arthritis (RA)
   For the management of the signs and symptoms of RA [see Clinical Studies (14.2)]

   1.3 Juvenile Rheumatoid Arthritis (JRA)
   For the management of the signs and symptoms of JRA in patients 2 years and older [see Clinical Studies (14.3)]

   1.4 Ankylosing Spondylitis (AS)
   For the management of the signs and symptoms of AS [see Clinical Studies (14.4)]

   1.5 Acute Pain
   For the management of acute pain in adults [see Clinical Studies (14.5)]

   1.6 Primary Dysmenorrhea
   For the management of primary dysmenorrhea [see Clinical Studies (14.5)]

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions
   Carefully consider the potential benefits and risks of CELEBREX and other treatment options before deciding to use CELEBREX. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)].

   These doses can be given without regard to timing of meals.

2.2 Osteoarthritis
   For OA, the dosage is 200 mg per day administered as a single dose or as 100 mg twice daily.

2.3 Rheumatoid Arthritis
   For RA, the dosage is 100 to 200 mg twice daily.

2.4 Juvenile Rheumatoid Arthritis
   For JRA, the dosage for pediatric patients (age 2 years and older) is based on weight. For patients ≥10 kg to <25 kg the recommended dose is 50 mg twice daily. For patients ≥25 kg the recommended dose is 100 mg twice daily.

   For patients who have difficulty swallowing capsules, the contents of a CELEBREX capsule can be added to applesauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions (2-8° C/ 35-45° F).

2.5 Ankylosing Spondylitis
   For AS, the dosage of CELEBREX is 200 mg daily in single (once per day) or divided (twice per day) doses. If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options.

2.6 Management of Acute Pain and Treatment of Primary Dysmenorrhea
   For management of Acute Pain and Treatment of Primary Dysmenorrhea, the dosage is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

2.7 Special Populations

   Hepatic Impairment
   In patients with moderate hepatic impairment (Child-Pugh Class B), reduce the dose by 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended [see Warnings and Precautions (5.5), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].
Poor Metabolizers of CYP2C9 Substrates

In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose.

In patients with JRA who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments. [see Use in Specific populations (8.8), and Clinical Pharmacology (12.5)].

3. DOSAGE FORMS AND STRENGTHS

CELEBREX (celecoxib) capsules:
- 50 mg white, with reverse printed white on red band of body and cap with markings of 7767 on the cap and 50 on the body.
- 100 mg white, with reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body.
- 200 mg white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body.
- 400 mg white, with reverse printed white on green band with markings of 7767 on the cap and 400 on the body.

4. CONTRAINDICATIONS

CELEBREX is contraindicated in the following patients:
- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to celecoxib, any components of the drug product [see Warnings and Precautions (5.7, 5.9)].
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs, have been reported in such patients [see Warnings and Precautions (5.7, 5.8)].
- In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)].
- In patients who have demonstrated allergic-type reactions to sulfonamides.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

In the APC (Adenoma Prevention with Celecox b) trial, the hazard ratio for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for CELEBREX 400 mg twice daily and 2.8 (95% CI 1.1 – 7.2) with CELEBREX 200 mg twice daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction [see Clinical Studies (14.6)].

To minimize the potential risk for an adverse CV event in CELEBREX-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as celecoxib, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of Celebrex in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If Celebrex is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including celecoxib cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with CELEBREX. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy are symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants; or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.
Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS trial, and 2.19% for the subgroup on low-dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA [see Clinical Studies (14.6)].

**Strategies to Minimize the GI Risks in NSAID-treated patients:**

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue CELEBREX until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see Drug Interactions (7)].

**5.3 Hepatotoxicity**

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminating hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including celecoxib.

In controlled clinical trials of CELEBREX, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue CELEBREX immediately, and perform a clinical evaluation of the patient.

**5.4 Hypertension**

NSAIDs, including CELEBREX can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics or loop diuretics may have impaired response to these therapies when taking NSAIDs [see Drug Interactions (7)].

The rates of hypertension from the CLASS trial in the CELEBREX, ibuprofen and diclofenac-treated patients were 2.4%, 4.2% and 2.5%, respectively [see Clinical Studies (14.6)].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

**5.5 Heart Failure and Edema**

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of celecoxib may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [see Drug Interactions (7)].

In the CLASS study [see Clinical Studies (14.6)], the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively.

Avoid the use of CELEBREX in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If CELEBREX is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

**5.6 Renal Toxicity and Hyperkalemia**

**Renal Toxicity**

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal dysfunction. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors or the ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of CELEBREX in patients with advanced renal disease. The renal effects of CELEBREX may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating CELEBREX. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of CELEBREX [see Drug Interactions (7)]. Avoid the use of CELEBREX in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If CELEBREX is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.
5.7 Anaphylactic Reactions
Celecoxib has been associated with anaphylactic reactions in patients with and without known hypersensitivity to celecoxib and in patients with aspirin sensitive asthma. Celecoxib is a sulfonamide and both NSAIDs and sulfonamides may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people [see Contraindications (4) and Warnings and Precautions (5.8)].

Seek emergency help if any anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, CELEBREX is contraindicated in patients with this form of aspirin sensitivity [see Contraindications (4)]. When CELEBREX is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions
Serious skin reactions have occurred following treatment with Celecoxib, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthemeatous pustulosis (AGEP). These serious events may occur without warning and can be fatal.

Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of CELEBREX at the first appearance of skin rash or any other sign of hypersensitivity. CELEBREX is contraindicated in patients with previous serious skin reactions to NSAIDs [see Contraindications (4)].

5.10 Premature Closure of Fetal Ductus Arteriosus
Celecoxib may cause premature closure of the ductus arteriosus. Avoid use of NSAIDs, including CELEBREX, in pregnant women starting at 30 weeks of gestation (third trimester) [see Use in Specific Populations (8.1)].

5.11 Hematological Toxicity
Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with CELEBREX has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs, including CELEBREX, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [see Drug Interactions (7)].

5.12 Masking of Inflammation and Fever
The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.13 Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [see Warnings and Precautions (5.2, 5.3, 5.6)].

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

5.14 Disseminated Intravascular Coagulation (DIC)
Because of the risk of disseminated intravascular coagulation with use of CELEBREX in pediatric patients with systemic onset JRA, monitor patients for signs and symptoms of abnormal clotting or bleeding, and inform patients and their caregivers to report symptoms as soon as possible.

6. ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Cardiovascular Thrombotic Events [see Warnings and Precautions (5.1)]
- GI Bleeding, Ulceration and Perforation [see Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Hypertension [see Warnings and Precautions (5.4)]
- Heart Failure and Edema [see Warnings and Precautions (5.5)]
- Renal Toxicity and Hyperkalemia [see Warnings and Precautions (5.6)]
- Anaphylactic Reactions [see Warnings and Precautions (5.7)]
- Serious Skin Reactions [see Warnings and Precautions (5.8)]
- Hematologic Toxicity [see Warnings and Precautions (5.11)]

Hypertension
Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic- hypoadosteronism state.

Renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic- hypoadosteronism state.

Aspirin sensitive asthma. Celebrex is a sulfonamide and both NSAIDs and sulfonamides may cause allergic type reactions including

Anaphylactic Reactions and life-threatening or less severe asthmatic episodes in certain susceptible people [see Contraindications (4) and Warnings and Precautions (5.8)].

Serious skin reactions have occurred following treatment with Celecoxib, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthemeatous pustulosis (AGEP). These serious events may occur without warning and can be fatal.

Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of CELEBREX at the first appearance of skin rash or any other sign of hypersensitivity. CELEBREX is contraindicated in patients with previous serious skin reactions to NSAIDs [see Contraindications (4)].

Serious Skin Reactions
Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with CELEBREX has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs, including CELEBREX, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [see Drug Interactions (7)].

Masking of Inflammation and Fever
The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [see Warnings and Precautions (5.2, 5.3, 5.6)].

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

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ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [see Warnings and Precautions (5.1)]
- GI Bleeding, Ulceration and Perforation [see Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Hypertension [see Warnings and Precautions (5.4)]
- Heart Failure and Edema [see Warnings and Precautions (5.5)]
- Renal Toxicity and Hyperkalemia [see Warnings and Precautions (5.6)]
- Anaphylactic Reactions [see Warnings and Precautions (5.7)]
- Serious Skin Reactions [see Warnings and Precautions (5.8)]
- Hematologic Toxicity [see Warnings and Precautions (5.11)]
6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Of the CELEBREX-treated patients in the pre-marketing controlled clinical trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients received a total daily dose of CELEBREX of 200 mg (100 mg twice daily or 200 mg once daily) or more, including more than 400 treated at 800 mg (400 mg twice daily). Approximately 3,900 patients received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Pre-marketing Controlled Arthritis Trials

Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group. Since these 12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

<table>
<thead>
<tr>
<th>Table 1: Adverse Events Occurring in ≥2% of CELEBREX Patients from Pre-marketing Controlled Arthritis Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Abdominal Pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Flatulence</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td><strong>Body as a whole</strong></td>
</tr>
<tr>
<td>Back Pain</td>
</tr>
<tr>
<td>Peripheral Edema</td>
</tr>
<tr>
<td>Injury-Accidental</td>
</tr>
<tr>
<td><strong>Central, Peripheral Nervous system</strong></td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Rinitis</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>

The following adverse reactions occurred in 0.1 - 1.9% of patients treated with CELEBREX (100 - 200 mg twice daily or 200 mg once daily):

- **Gastrointestinal**: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, vomiting
- **Cardiovascular**: Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction
- **General**: Hypersensitivity, allergic reaction, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain
- **Central, peripheral**: Leg cramps, hypertonia, hypothysema, nervous system: migraine, paresthesia, vertigo
- **Hearing and vestibular**: Deafness, tinnitus

**Heart rate and rhythm**: Palpitation, tachycardia

**Liver and biliary**: Hepatic enzyme increased (including SGOT increased, SGPT increased)

**Metabolic and nutritional**: BUN increased, CPK increased, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increased, creatinine increased, alkaline phosphatase increased, weight increased

**Musculoskeletal**: Arthralgia, arthritis, myalgia, synovitis, tendinitis

**Platelets (bleeding or clotting)**: Ecchymosis, epistaxis, thrombocythemia

**Psychiatric**: Anorexia, anxiety, appetite increased, depression, nervousness, somnolence

**Hemic**: Anemia

**Respiratory**: Bronchitis, bronchospasm, bronchospasm aggravated, cough, dyspnea, laryngitis, pneumonia

**Skin and appendages**: Alopecia, dermatitis, photosensitivity, reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria

**Application site disorders**: Cellulitis, dermatitis contact

**Urinary**: A buminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus

The following serious adverse events (causality not evaluated) occurred in <0.1% of patients:

**Cardiovascular**: Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis
Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus

General: Sepsis, sudden death

Liver and biliary: Cholelithiasis

Hemic and lymphatic: Thrombocytopenia

Nervous: Ataxia, suicide [see Drug Interactions (7.1)]

Renal: Acute renal failure

The Celecoxib Long-Term Arthritis Safety Study [see Special Studies (14.6)]

Hematological Events: The incidence of clinically significant decreases in hemoglobin (>2 g/dL) was lower in patients on CELEBREX 400 mg twice daily (0.5%) compared to patients on either diclofenac 75 mg twice daily (1.3%) or ibuprofen 800 mg three times daily 1.9%. The lower incidence of events with CELEBREX was maintained with or without aspirin use [see Clinical Pharmacology (12.2)].

Withdrawals/Serious Adverse Events: Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for CELEBREX, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (i.e., causing hospitalization or felt to be life-threatening or otherwise medically significant), regardless of causality, were not different across treatment groups (8%, 7%, and 8%, respectively).

Juvenile Rheumatoid Arthritis Study

In a 12-week, double-blind, active-controlled study, 242 JRA patients 2 years to 17 years of age were treated with celecoxib or naproxen; 77 JRA patients were treated with celecoxib 3 mg/kg twice daily, 82 patients were treated with celecoxib 6 mg/kg twice daily, and 83 patients were treated with naproxen 7.5 mg/kg twice daily. The most commonly occurring (≥5%) adverse events in celecoxib treated patients were headache, fever (pyrexia), upper abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhea and vomiting. The most commonly occurring (≥5%) adverse experiences for naproxen-treated patients were headache, nausea, vomiting, fever, upper abdominal pain, diarrhea, cough, abdominal pain, and dizziness (Table 2). Compared with naproxen, celecoxib at doses of 3 and 6 mg/kg twice daily had no observable deleterious effect on growth and development during the course of the 12-week double-blind study. There was no substantial difference in the number of clinical exacerbations of uveitis or systemic features of JRA among treatment groups.

In a 12-week, open-label extension of the double-blind study described above, 202 JRA patients were treated with celecoxib 6 mg/kg twice daily. The incidence of adverse events was similar to that observed during the double-blind study; no unexpected adverse events of clinical importance emerged.

Table 2: Adverse Events Occurring in ≥5% of JRA Patients in Any Treatment Group, by System Organ Class (% of patients with events)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Celecoxib 3 mg/kg</th>
<th>Celecoxib 6 mg/kg</th>
<th>Naproxen 7.5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>64</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>26</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Abdominal pain NOS</td>
<td>4</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>8</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting NOS</td>
<td>3</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea NOS</td>
<td>5</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>General</td>
<td>13</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Infections</td>
<td>25</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Injury and Poisoning</td>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Investigations*</td>
<td>3</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>8</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Nervous System</td>
<td>17</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Headache NOS</td>
<td>13</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Dizziness (excl vertigo)</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Respiratory</td>
<td>8</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Cough</td>
<td>7</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Skin &amp; Subcutaneous</td>
<td>10</td>
<td>7</td>
<td>18</td>
</tr>
</tbody>
</table>

* Abnormal laboratory tests, which include: Prolonged activated partial thromboplastin time, Bacteriuria NOS present, Blood creatine phosphokinase increased, Blood culture positive, Blood glucose increased, Blood pressure increased, Blood uric acid increased, Hematocrit decreased, Hematuria present, Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS increased, Urine analysis abnormal NOS
Other Pre-Approval Studies

**Adverse Events from Ankylosing Spondylitis Studies:** A total of 378 patients were treated with CELEBREX in placebo- and active-controlled AS studies. Doses up to 400 mg once daily were studied. The types of adverse events reported in the AS studies were similar to those reported in the OA/RA studies.

**Adverse Events from Analgesia and Dysmenorrhea Studies:** Approximately 1,700 patients were treated with CELEBREX in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medication. Doses up to 600 mg/day of CELEBREX were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

The APC and PreSAP Trials

**Adverse reactions from long-term, placebo-controlled polyp prevention studies:** Exposure to CELEBREX in the APC and PreSAP trials was 400 to 800 mg daily for up to 3 years [see Special Studies Adenomatous Polyp Prevention Studies (14.6)].

Some adverse reactions occurred in higher percentages of patients than in the arthritis pre-marketing trials (treatment durations up to 12 weeks; see Adverse events from CELEBREX pre-marketing controlled arthritis trials, above). The adverse reactions for which these differences in patients treated with CELEBREX were greater as compared to the arthritis pre-marketing trials were as follows:

<table>
<thead>
<tr>
<th></th>
<th>CELEBREX (400 to 800 mg daily)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 2285</td>
<td>N=1303</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.5%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>4.7%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.8%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.8%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12.5%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>2.1%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

The following additional adverse reactions occurred in ≥0.1% and <1% of patients taking CELEBREX, at an incidence greater than placebo in the long-term polyp prevention studies, and were either not reported during the controlled arthritis pre-marketing trials or occurred with greater frequency in the long-term, placebo-controlled polyp prevention studies:

**Nervous system disorders:** Cerebral infarction

**Eye disorders:** Vitreous floaters, conjunctival hemorrhage

**Ear and labyrinth:** Labyrinthitis

**Cardiac disorders:** Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy

**Vascular disorders:** Deep vein thrombosis

**Reproductive system and breast disorders:** Ovarian cyst

**Investigations:** Blood potassium increased, blood sodium increased, blood testosterone decreased

**Injury, poisoning and procedural complications:** Epicondylitis, tendon rupture

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of CELEBREX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure

**Cardiovascular:** Vasculitis, deep venous thrombosis

**General:** Anaphylactoid reaction, angioedema

**Liver and biliary:** Liver necrosis, hepatitis, jaundice, hepatic failure

**Hemic and lymphatic:** Agranulocytosis, aplastic anemia, pancytopenia, leukopenia

**Metabolic:** Hypoglycemia, hyponatremia

**Nervous:** Aseptic meningitis, ageusia, anosmia, fatal intracranial hemorrhage

**Renal:** Interstitial nephritis
7. DRUG INTERACTIONS

See Table 3 for clinically significant drug interactions with celecoxib.

Table 3: Clinically Significant Drug Interactions with Celecoxib

<table>
<thead>
<tr>
<th>Drugs That Interfere with Hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>• Celecoxib and antiocoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of Celecoxib and antiocoagulants have an increased risk of serious bleeding compared to the use of either drug alone.</td>
</tr>
<tr>
<td>• Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>Monitor patients with concomitant use of CELEBREX with antiocoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin noradrenaline reuptake inhibitors (SNRIs) for signs of bleeding [see Warnings and Precautions (5.11)].</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
</tr>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td>In two studies in healthy volunteers, and in patients with osteoarthritis and established heart disease respectively, celecoxib (200-400 mg daily) has demonstrated a lack of interference with the cardioprotective antiplatelet effect of aspirin (100-325 mg).</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>Concomitant use of CELEBREX and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [see Warnings and Precautions (5.11)].</td>
</tr>
<tr>
<td>CELEBREX is not a substitute for low dose aspirin for cardiovascular protection.</td>
</tr>
<tr>
<td><strong>ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers</strong></td>
</tr>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).</td>
</tr>
<tr>
<td>• In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, con administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>During concomitant use of CELEBREX and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.</td>
</tr>
<tr>
<td>During concomitant use of CELEBREX and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [see Warnings and Precautions (5.6)].</td>
</tr>
<tr>
<td>• When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
</tr>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>During concomitant use of CELEBREX with diuretics, observe patients for signs of worsening renal function, in addition to assessing diuretic efficacy including antihypertensive effects [see Warnings and Precautions (5.6)].</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
</tr>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>The concomitant use of Celecoxib with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>During concomitant use of CELEBREX and digoxin, monitor serum digoxin levels.</td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
</tr>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>During concomitant use of CELEBREX and lithium, monitor patients for signs of lithium toxicity.</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
</tr>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).</td>
</tr>
<tr>
<td>Celecoxib has no effect on methotrexate pharmacokinetics.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>During concomitant use of CELEBREX and methotrexate, monitor patients for methotrexate toxicity.</td>
</tr>
<tr>
<td><strong>Cyclosporine</strong></td>
</tr>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>Concomitant use of CELEBREX and cyclosporine may increase cyclosporine's nephrotoxicity.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>During concomitant use of CELEBREX and cyclosporine, monitor patients for signs of worsening renal function.</td>
</tr>
</tbody>
</table>
**NSAIDs and Salicylates**

| Clinical Impact | Concomitant use of Celecoxib with other NSAIDs or salicylates (e.g., diflunisal, salicylate) increases the risk of GI toxicity, with little or no increase in efficacy [see Warnings and Precautions (5.2)]. |
| Intervention | The concomitant use of Celecoxib with other NSAIDs or salicylates is not recommended. |

**Pemetrexed**

| Clinical Impact | Concomitant use of CELEBREX and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information). |
| Intervention | During concomitant use of CELEBREX and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration. |

**CYP2C9 Inhibitors or Inducers**

| Clinical Impact | Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 (e.g. fluconazole) may enhance the exposure and toxicity of celecoxib whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of celecoxib. |
| Intervention | Evaluate each patient’s medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers. [see Clinical Pharmacology (12.3)] |

**CYP2D6 substrates**

| Clinical Impact | In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6 (e.g. alomoxetine), and celecoxib may enhance the exposure and toxicity of these drugs. |
| Intervention | Evaluate each patient’s medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2D6 substrates. [see Clinical Pharmacology (12.3)] |

**Corticosteroids**

| Clinical Impact | Concomitant use of corticosteroids with CELEBREX may increase the risk of GI ulceration or bleeding. |
| Intervention | Monitor patients with concomitant use of CELEBREX with corticosteroids for signs of bleeding [see Warnings and Precautions (5.2)] |

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Pregnancy category D from 30 weeks of gestation onward.

**Risk Summary**

Use of NSAIDs, including CELEBREX, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including CELEBREX, in pregnant women starting at 30 weeks of gestation.

There are no adequate and well-controlled studies of CELEBREX in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2.4% for major malformations, and 15.20% for pregnancy loss. In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 6 times the maximum recommended human dose of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternum fused and sternum missmash) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 2 times the MRHD [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as celecoxib, resulted in increased pre- and post-implantation loss.

**Clinical Considerations**

**Labor or Delivery**

There are no studies on the effects of CELEBREX during labor or delivery. In animal studies, NSAIDs, including celecoxib, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

**Data**

**Human Data**

The available data do not establish the presence or absence of developmental toxicity related to the use of Celebrex.

**Animal data**

Celecoxib at oral doses ≥150 mg/kg/day (approximately 2 times the human exposure at 200 mg twice daily as measured by AUC0-24), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternum fused and sternum missmash when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6 times human exposure based on the AUC0-24 at 200 mg twice daily for RA) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in
pre-implantation and post-implantation losses at oral doses $\geq$50 mg/kg/day (approximately 6 times human exposure based on the AUC$_{0-24}$ at 200 mg twice daily for RA).

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC$_{0-24}$ at 200 mg twice daily). The effects of CELEBREX on labor and delivery in pregnant women are unknown.

8.2 Lactation

Risk Summary
Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of CELEBREX in breast milk. The calculated average daily infant dose was 10-40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when CELEBREX is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CELEBREX and any potential adverse effects on the breastfed infant from the CELEBREX or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Females
Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including CELEBREX, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including CELEBREX, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

CELEBREX is approved for relief of the signs and symptoms of Juvenile Rheumatoid Arthritis in patients 2 years and older. Safety and efficacy have not been studied beyond six months in children. The long-term cardiovascular toxicity in children exposed to CELEBREX has not been evaluated and it is unknown if long-term risks may be similar to that seen in adults exposed to CELEBREX or other COX-2 selective and non-selective NSAIDs [see Boxed Warning, Warnings and Precautions (5.12), and Clinical Studies (14.3)].

The use of celecoxib in patients 2 years to 17 years of age with pauciarticular, polyarticular course JRA or in patients with systemic onset JRA was studied in a 12-week, double-blind, active controlled, pharmacokinetic, safety and efficacy study, with a 12-week open-label extension. Celecoxib has not been studied in patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features. Patients with systemic onset JRA (without active systemic features) appear to be at risk for the development of abnormal coagulation laboratory tests. In some patients with systemic onset JRA, both celecoxib and naproxen were associated with mild prolongation of activated partial thromboplastin time (APTT) but not prothrombin time (PT). When NSAIDs including celecoxib are used in patients with systemic onset JRA, monitor patients for signs and symptoms of abnormal clotting or bleeding, due to the risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests [see Dosage and Administration (2.4), Warnings and Precautions (5.12), Adverse Reactions (6.3), Animal Toxicology (13.2), Clinical Studies (14.3)].

Alternative therapies for treatment of JRA should be considered in pediatric patients identified to be CYP2C9 poor metabolizers [see Poor Metabolizers of CYP2C9 substrates (8.8)].

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.13)].

Of the total number of patients who received CELEBREX in pre-approval clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and younger patients. However, as with other NSAIDs, including CELEBREX, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients [see Warnings and Precautions (5.4, 5.6)].

8.6 Hepatic Impairment

The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended [see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)].

8.7 Renal Impairment

CELEBREX is not recommended in patients with severe renal insufficiency [see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)].

8.8 Poor Metabolizers of CYP2C9 Substrates

In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*3/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) administer CELEBREX starting with half the lowest recommended dose. Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers. [see Dosage and Administration (2.6) and Clinical Pharmacology (12.5)].
10. OVERDOSE
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)].

No overdoses of CELEBREx were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose.

Manage patients with symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdose (5 to 10 times the recommended dosage). Forced diuresis, a kaliuresis of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdose treatment contact a poison control center (1-800-222-1222).

11. DESCRIPTION
CELEBREX (celecoxib) capsule is a nonsteroidal anti-inflammatory drug, available as capsules containing 50 mg, 100 mg, 200 mg and 400 mg celecoxib for oral administration. The chemical name is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl substituted pyrazole. The molecular weight is 381.38. Its molecular formula is C$_{15}$H$_{14}$F$_3$N$_2$O$_5$S$_2$ and it has the following chemical structure:

![Chemical Structure of Celecoxib](image)

Celecoxib is a white to off-white powder with a pKa of 11.1 (sulfonamide moiety). Celecoxib is hydrophobic (log P is 3.5) and is practically insoluble in aqueous media at physiological pH range.

The inactive ingredients in CELEBREX include: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone and sodium lauryl sulfate.

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
CELEBREX has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2).

Celecoxib is a potent inhibitor of prostaglandin synthesis in vitro. Celecoxib concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since celecoxib is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacodynamics

Platelets
In clinical trials using normal volunteers, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg twice daily for up to 7 days duration (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time. Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of CELEBREX on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of CELEBREX.

Fluid Retention
Inhibition of PGE2 synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PGE2 appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.
12.3 Pharmacokinetics

Celecoxib exhibits dose-proportional increase in exposure after oral administration up to 200 mg twice daily and less than proportional increase at higher doses. It has extensive distribution and high protein binding. It is primarily metabolized by CYP2C9 with a half-life of approximately 11 hours.

Absorption

Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose-proportional up to 200 mg twice daily; at higher doses there are less than proportional increases in Cmax and AUC [see Food Effects]. Absolute bioavailability studies have not been conducted. With multiple dosing, steady-state conditions are reached on or before Day 5. The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 4.

Table 4
Summary of Single Dose (200 mg) Disposition
Kinetics of Celecoxib in Healthy Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (%CV) PK Parameter Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>705 (38)</td>
</tr>
<tr>
<td>Tmax, hr</td>
<td>2.8 (37)</td>
</tr>
<tr>
<td>Effective t1/2, hr</td>
<td>11.2 (31)</td>
</tr>
<tr>
<td>Vss/F, L</td>
<td>429 (34)</td>
</tr>
<tr>
<td>CL/F, L/hr</td>
<td>27.7 (28)</td>
</tr>
</tbody>
</table>

Food Effects

When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in Cmax and AUC, which is thought to be due to the low solubility of the drug in aqueous media.

Coadministration of CELEBREX with an aluminum- and magnesium-containing antacids resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC. CELEBREX, at doses up to 200 mg twice daily, can be administered without regard to timing of meals. Higher doses (400 mg twice daily) should be administered with food to improve absorption.

In healthy adult volunteers, the overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in Cmax, Tmax or t1/2 after administration of capsule contents on applesauce [see Dosage and Administration (2)].

Distribution

In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. In vitro studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, a-1-acid glycoprotein. The apparent volume of distribution at steady state (Vss/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Elimination

Metabolism

Celecoxib metabolism is primarily mediated via CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors.

Excretion

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life (t1/2) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Specific Populations

Geriatric

At steady state, elderly subjects (over 65 years old) had a 40% higher Cmax and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib Cmax and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose [see Dosage and Administration (2.7) and Use in Specific Populations (8.5)].

Pediatric

The steady state pharmacokinetics of celecoxib administered as an investigational oral suspension was evaluated in 152 JRA patients 2 years to 17 years of age weighing ≥10 kg with pauciarticular or polyarticular course JRA and in patients with systemic onset JRA. Population pharmacokinetic analysis indicated that the oral clearance (unadjusted for body weight) of celecoxib increases less than proportionally to increasing weight, with 10 kg and 25 kg patients predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg adult RA patient.

Twice-daily administration of 50 mg capsules to JRA patients weighing ≥12 to ≤25 kg and 100 mg capsules to JRA patients weighing >25 kg should achieve plasma concentrations similar to those observed in a clinical trial that demonstrated the non-inferiority of celecoxib to naproxen 7.5 mg/kg twice daily [see Dosage and Administration (2.4)]. Celecoxib has not been studied in JRA patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), or beyond 24 weeks.
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13.2 Animal Toxicology

12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *1/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups. [see Dosage and Administration (2.6), Use in Specific Populations (8.8)].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Celecoxib was not carcinogenic in Sprague-Dawley rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-times the human exposure as measured by the AUC0-24 at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC0-24 at 200 mg twice daily) for two years.

Mutagenesis

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an in vivo micronucleus test in rat bone marrow.

Impairment of Fertility

Celecoxib had no effect on male or female fertility or male reproductive function in rats at oral doses up to 600 mg/kg/day (approximately 11-times human exposure at 200 mg twice daily based on the AUC0-24). At ≥50 mg/kg/day (approximately 6-times human exposure based on the AUC0-24 at 200 mg twice daily) there was increased preimplantation loss.

13.2 Animal Toxicology

An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight dilation of the seminiferous tubules was seen in the juvenile rat. These reproductive findings while apparently treatment-related did not increase in incidence or severity with dose and may indicate an exacerbation of a spontaneous condition. Similar reproductive findings were not observed in studies of juvenile or adult dogs or in adult rats treated with celecoxib. The clinical significance of this observation is unknown.
14. CLINICAL STUDIES

14.1 Osteoarthritis

CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA treated with CELEBREX 100 mg twice daily or 200 mg once daily, improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures, was demonstrated in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100 mg twice daily and 200 mg twice daily provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg twice daily or 200 mg twice daily the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg twice daily. Doses of 200 mg twice daily provided no additional benefit above that seen with 100 mg twice daily. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg twice daily or 200 mg once daily.

14.2 Rheumatoid Arthritis

CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of 100 mg twice daily and 200 mg twice daily were similar in effectiveness and both were comparable to naproxen 500 mg twice daily.

Although CELEBREX 100 mg twice daily and 200 mg twice daily provided similar overall effectiveness, some patients derived additional benefit from the 200 mg twice daily dose. Doses of 400 mg twice daily provided no additional benefit above that seen with 100-200 mg twice daily.

14.3 Juvenile Rheumatoid Arthritis

In a 12-week, randomized, double-blind active-controlled, parallel-group, multicenter, non-inferiority study, patients from 2 years to 17 years of age with pauciarticular, polyarticular course JRA or systemic onset JRA (with currently inactive systemic features), received one of the following treatments: celecoxib 3 mg/kg (to a maximum of 150 mg) twice daily; celecoxib 6 mg/kg (to a maximum of 300 mg) twice daily; or naproxen 7.5 mg/kg (to a maximum of 500 mg) twice daily. The response rates were based upon the JRA Definition of Improvement greater than or equal to 30% (JRA DOI 30) criterion, which is a composite of clinical, laboratory, and functional measures of JRA. The JRA DOI 30 response rates at week 12 were 69%, 80% and 67% in the celecoxib 3 mg/kg twice daily, celecoxib 6 mg/kg twice daily, and naproxen 7.5 mg/kg twice daily treatment groups, respectively.

The efficacy and safety of CELEBREX for JRA have not been studied beyond six months. The long-term cardiovascular toxicity in children exposed to CELEBREX has not been evaluated and it is unknown if the long-term risk may be similar to that seen in adults exposed to CELEBREX or other COX-2 selective and non-selective NSAIIDs [[see Boxed Warning, Warnings and Precautions (5.12)].

14.4 Ankylosing Spondylitis

CELEBREX was evaluated in AS patients in two placebo- and active-controlled clinical trials of 6 and 12 weeks duration. CELEBREX at doses of 100 mg twice daily, 200 mg once daily and 400 mg once daily was shown to be statistically superior to placebo in these studies for all three co-primary efficacy measures assessing global pain intensity (Visual Analogue Scale), global disease activity (Visual Analogue Scale) and functional impairment (Bath Ankylosing Spondylitis Functional Index). In the 12-week study, there was no difference in the extent of improvement between the 200 mg and 400 mg CELEBREX doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to CELEBREX 400 mg, 53%, than to CELEBREX 200 mg, 44%, using the Assessment in Ankylosing Spondylitis response criteria (ASAS 20). The ASAS 20 defines a responder as improvement from baseline of at least 20% and an absolute improvement of at least 10 mm, on a 0 to 100 mm scale, in at least three of the four following domains: patient global pain, Bath Ankylosing Spondylitis Functional Index, and inflammation. The responder analysis also demonstrated no change in the responder rates beyond 6 weeks.

14.5 Analgesia, including Primary Dysmenorrhea

In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, CELEBREX relieved pain that was rated by patients as moderate to severe. Single doses [see Dosage and Administration (2.6)] of CELEBREX provided pain relief within 60 minutes.

14.6 Special Studies

Adenomatous Polypl Prevention Studies

Cardiovascular safety was evaluated in two randomized, double-blind, placebo-controlled, three year studies involving patients with Sporadic Adenomatous Polyps treated with CELEBREX: the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint (adjudicated):

- In the APC trial, the hazard ratios compared to placebo for a composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke were 3.4 (95% CI 1.4 - 8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1 - 7.2) with celecoxib 200 mg twice daily. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction.
- In the PreSAP trial, the hazard ratio for this same composite endpoint (adjudicated) was 1.2 (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 2.3% (21/933 subjects) and 1.9% (12/628 subjects), respectively.

Clinical trials of other COX-2 selective and non-selective NSAIDs of up to three-years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. As a result, all NSAIDs are considered potentially associated with this risk.
Celecoxib Long-Term Arthritis Safety Study (CLASS)
This was a prospective, long-term, safety outcome study conducted post-marketing in approximately 5,800 OA patients and 2,200 RA patients. Patients received CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily (common therapeutic doses). Median exposures for CELEBREX (n = 3,987) and diclofenac (n = 1,996) were 9 months while ibuprofen (n = 1,985) was 6 months. The primary endpoint of this outcome study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation or obstruction). Patients were allowed to take concomitant low-dose (< 325 mg/day) aspirin (ASA) for cardiovascular prophylaxis (ASA subgroups: CELEBREX, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of complicated ulcers between CELEBREX and the combined group of ibuprofen and diclofenac were not statistically significant.

Patients on CELEBREX and concomitant low-dose ASA (N=882) experienced 4-fold higher rates of complicated ulcers compared to those not on ASA (N=3105). The Kaplan-Meier rate for complicated ulcers at 9 months was 1.12% versus 0.32% for those on low-dose ASA and those not on ASA, respectively [see Warnings and Precautions (5.4)].

The estimated cumulative rates at 9 months of complicated and symptomatic ulcers for patients treated with CELEBREX 400 mg twice daily are described in Table 4. Table 4 also displays results for patients less than or greater than 65 years of age. The difference in rates between CELEBREX alone and CELEBREX with ASA groups may be due to the higher risk for GI events in ASA users.

| Table 5: Complicated and Symptomatic Ulcer Rates in Patients Taking CELEBREX 400 mg Twice Daily (Kaplan-Meier Rates at 9 months [%]) Based on Risk Factors |
|---------------------------------|-----------------|-----------------|
| All Patients                    |                 |                 |
| CELEBREX alone (n=3105)         | 0.78            |                 |
| CELEBREX with ASA (n=882)       | 2.19            |                 |
| Patients <65 Years              |                 |                 |
| CELEBREX alone (n=2025)         | 0.47            |                 |
| CELEBREX with ASA (n=403)       | 1.26            |                 |
| Patients ≥65 Years              |                 |                 |
| CELEBREX alone (n=1080)         | 1.40            |                 |
| CELEBREX with ASA (n=479)       | 3.06            |                 |

In a small number of patients with a history of ulcer disease, the complicated and symptomatic ulcer rates in patients taking CELEBREX alone or CELEBREX with ASA were, respectively, 2.56% (n=243) and 6.85% (n=91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease [see Warnings and Precautions (5.4) and Adverse Reactions (6.1)].

Cardiovascular safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier cumulative rates for investigator-reported serious cardiovascular thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated no differences between the CELEBREX, diclofenac, or ibuprofen treatment groups. The cumulative rates in all patients at nine months for CELEBREX, diclofenac, and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The cumulative rates in non-ASA users at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in non-ASA users at nine months in each of the three treatment groups were less than 0.2%. There was no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased the risk to a similar degree.

Endoscopic Studies
The correlation between findings of short-term endoscopic studies with CELEBREX and the relative incidence of clinically significant serious upper GI events with long-term use has not been established. Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open-labeled trials [see Warnings and Precautions (5.4) and Clinical Studies (14.6)].

A randomized, double-blind study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers in patients taking CELEBREX 200 mg twice daily was 4% vs. 15% for patients taking diclofenac SR 75 mg twice daily. However, CELEBREX was not statistically different than diclofenac for clinically relevant GI outcomes in the CLASS trial [see Clinical Studies (14.6)].

The incidence of endoscopic ulcers was studied in two 12-week, placebo-controlled studies in 2157 OA and RA patients in whom baseline endoscopies revealed no ulcers. There was no dose relationship for the incidence of gastrodudenal ulcers and the dose of CELEBREX (50 mg to 400 mg twice daily). The incidence for naproxen 500 mg twice daily was 16.2 and 17.6% in the two studies, for placebo was 2.0 and 2.3%, and for all doses of CELEBREX the incidence ranged between 2.7%-5.9%. There have been no large, clinical outcome studies to compare clinically relevant GI outcomes with CELEBREX and naproxen.

In the endoscopic studies, approximately 11% of patients were taking aspirin (< 325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.
16. HOW SUPPLIED/STORAGE AND HANDLING

CELEBREX (celecoxib) 50 mg capsules are white, with reverse printed white on red band of body and cap with markings of 7767 on the cap and 50 on the body, supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0025-1515-01</td>
<td>bottle of 60</td>
</tr>
</tbody>
</table>

CELEBREX (celecoxib) 100 mg capsules are white, with reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body, supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0025-1520-31</td>
<td>bottle of 100</td>
</tr>
<tr>
<td>0025-1520-51</td>
<td>bottle of 500</td>
</tr>
<tr>
<td>0025-1520-34</td>
<td>carton of 100 unit dose</td>
</tr>
</tbody>
</table>

CELEBREX (celecoxib) 200 mg capsules are white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body, supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0025-1525-31</td>
<td>bottle of 100</td>
</tr>
<tr>
<td>0025-1525-51</td>
<td>bottle of 500</td>
</tr>
<tr>
<td>0025-1525-34</td>
<td>carton of 100 unit dose</td>
</tr>
</tbody>
</table>

CELEBREX (celecoxib) 400 mg capsules are white, with reverse printed white on green band with markings of 7767 on the cap and 400 on the body, supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0025-1530-02</td>
<td>bottle of 60</td>
</tr>
<tr>
<td>0025-1530-01</td>
<td>carton of 100 unit dose</td>
</tr>
</tbody>
</table>

Storage
Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]

17. PATIENT COUNSELING INFORMATION

Advises the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with CELEBREX and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events
Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see Warnings and Precautions (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation
Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [see Warnings and Precautions (5.2)].

Hepatotoxicity
Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop CELEBREX and seek immediate medical therapy [see Warnings and Precautions (5.3), Use in Specific Populations (8.6)].

Heart Failure and Edema
Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see Warnings and Precautions (5.5)].

Anaphylactic Reactions
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [see Contraindications (4) and Warnings and Precautions (5.7)].

Serious Skin Reactions
Advise patients to stop CELEBREX immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [see Warnings and Precautions (5.9)].

Female Fertility
Advise females of reproductive potential who desire pregnancy that NSAIDs, including CELEBREX, may be associated with a reversible delay in ovulation [see Use in Specific Populations (8.3)].

Fetal Toxicity
Inform pregnant women to avoid use of CELEBREX and other NSAIDs starting at 30 weeks of gestation because of the risk of the premature closing of the fetal ductus arteriosus [see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)].
Avoid Concomitant Use of NSAIDs
Inform patients that the concomitant use of CELEBREX with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see Warnings and Precautions (5.2) and Drug Interactions (7)]. Alert patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concomitantly with CELEBREX until they talk to their healthcare provider [see Drug Interactions (7)].
What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft (CABG).”

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

NSAIDs should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?
NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDS, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy.
  - **You should not take NSAIDs after 29 weeks of pregnancy**
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your healthcare provider first.
What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescr bed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, ta k with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Manufactured for: Pfizer Inc., 235 East 42nd Street, New York, NY, 10017
Distributed by: G. D. Searle LLC, Division of Pfizer Inc., 235 East 42nd Street, New York, NY, 10017
For more information, go to www.pfizer.com or call 1-800-438-1985

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Issued: May 2016
LAB number: LAB-0609-1.x
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS safely and effectively. See full prescribing information for NAPROSYN, EC-NAPROSYN and ANAPROX DS.

NAPROSYN® (naproxen) tablets, EC-NAPROSYN® (naproxen delayed-release tablets), ANAPROX® DS (naproxen sodium tablets), for oral use

Initial U.S. Approval: 1976

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

• Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. (5 1)
• NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS are contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1, 5.3, 5.5)
• NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5 1, 5.3)

RECENT MAJOR CHANGES

Boxed Warning Warnings and Precautions (5.1, 5.5) 05/2016

INDICATIONS AND USAGE

the relief of the signs and symptoms of:

• rheumatoid arthritis
• osteoarthritis
• ankylosing spondylitis
• polyarticular juvenile idiopathic arthritis

NAPROSYN Tablets and ANAPROX DS are also indicated for:

the relief of signs and symptoms of:

• tendonitis
• bursitis
• acute gout

the management of:

• pain
• primary dysmenorrhea

DOSAGE AND ADMINISTRATION

Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1)

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis

NAPROSYN Tablets
250 mg (one-half tablet) 500 mg twice daily
ANAPROX DS 275 mg (one-half tablet) 550 mg twice daily
EC-NAPROSYN 375 mg or 500 mg twice daily

To maintain the integrity of the enteric coating, the EC-NAPROSYN tablet should not be broken, crushed or chewed during ingestion

The dose may be adjusted up or down depending on the clinical response of the patient. In patients who tolerate lower doses well, the dose may be increased to naproxen 1500 mg/day for up to 6 months

Polyarticular Juvenile Idiopathic Arthritis

NAPROSYN Tablets may not allow for the flexible dose titration needed in pediatric patients with polyarticular juvenile idiopathic arthritis. A liquid formulation may be more appropriate. Recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses. Dosing with NAPROSYN Tablets is not appropriate for children weighing less than 50 kilograms

Dosage and Administration

Recommended starting dose 550 mg of naproxen sodium as ANAPROX DS followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as required. The initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. ANAPROX DS is recommended for the management of acute painful conditions when prompt onset of pain relief is desired

Acute Gout
Recommended starting dose 750 mg of NAPROSYN Tablets followed by 250 mg every 8 hours until the attack has subsided. ANAPROX DS may also be used at a starting dose of 825 mg followed by 275 mg every 8 hours. EC-NAPROSYN is not recommended because of the delay in absorption.

DOSE FORMS AND STRENGTHS

NAPROSYN™ (naproxen) tablets: 500 mg
EC-NAPROSYN™ (naproxen) delayed-release tablets: 375 mg and 500 mg
ANAPROX® DS (naproxen sodium) tablets: 550 mg (contains 50 mg of sodium)

CONTRAINDICATIONS

• Known hypersensitivity to naproxen or any components of the drug product (4)
• History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
• In the setting of CABG surgery (4)

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)

Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)

Heart Failure and Edema: Avoid use of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)

Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)

Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)

Exacerbation of Asthma Related to Aspirin Sensitivity: Avoid use of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)

Serious Skin Reactions: Discontinue NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS at first appearance of skin rash or other signs of hypersensitivity (5.29)

Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.3)

Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

ADVERSE REACTIONS

Most common adverse reactions to naproxen were dyspepsia, abdominal pain, nausea, headache, rash, ecchymosis, and edema (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Canton Laboratories LLC at 1-844-302-5227 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS with drugs that interfere with hemostasis. Concomitant use of NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS and anagrelide doses of aspirin is not generally recommended (7)

ACE inhibitors, Angiotensin Receptor Blockers (ARBs), or Beta-Blockers: Concomitant use with NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)

ACE Inhibitors and ARBs: Concomitant use with NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)

Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients for bleeding who are concomitantly taking NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS with drugs that interfere with hemostasis. Concomitant use of NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)

ACE Inhibitors and ARBs: Concomitant use with NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)

Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients who are concomitantly taking NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS with drugs that interfere with hemostasis. Concomitant use of NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)

DIAGNOSTIC TESTS: NSAIDs can cause serious adverse reactions (e.g. neutropenia, anemia, and abnormal liver function tests). Monitor patients for abnormal liver tests or anemia when taking NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS (7)

USE IN SPECIFIC POPULATIONS

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.10, 8.1)

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS in women who have difficulties conceiving (8.3)

Renal Impairment: Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min) (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: [03/2017]
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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events
- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [see Warnings and Precautions (5.1)].
- NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications (4), Warnings and Precautions (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE
NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS are indicated for:
The relief of the signs and symptoms of:
- rheumatoid arthritis
- osteoarthritis
- ankylosing spondylitis
- Polyarticular Juvenile Idiopathic Arthritis

NAPROSYN Tablets and ANAPROX DS are also indicated for:
The relief of signs and symptoms of:
- tendonitis
- bursitis
- acute gout

the management of:
- pain
- primary dysmenorrhea

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Instructions
Carefully consider the potential benefits and risks of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS and other treatment options before deciding to use NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)].

After observing the response to initial therapy with NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS, the dose and frequency should be adjusted to suit an individual patient’s needs.
To maintain the integrity of the enteric coating, the EC-NAPROSYN tablet should not be broken, crushed or chewed during ingestion.

Naproxen-containing products such as NAPROSYN, EC-NAPROSYN and ANAPROX DS, and other naproxen products should not be used concomitantly since they all circulate in the plasma as the naproxen anion.

2.2 Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

The recommended dosages of NAPROSYN Tablets, ANAPROX DS, and EC-NAPROSYN are shown in Table 1.

| Table 1: Recommended dosages for NAPROSYN Tablets, ANAPROX DS, and EC-NAPROSYN |
|-----------------------------------------------|-----------------|------------------|
| NAPROSYN                                      | 250 mg (one half tablet) | 500 mg twice daily |
| ANAPROX DS                                    | 275 mg (one half tablet) | 550 mg (naproxen 500 mg with 50 mg sodium) twice daily |
| EC-NAPROSYN                                   | 375 mg or 500 mg | twice daily twice daily |

During long-term administration, the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary.

The morning and evening doses do not have to be equal in size and administration of the drug more frequently than twice daily does not generally make a difference in response.

In patients who tolerate lower doses well, the dose may be increased to naproxen 1500 mg/day for limited periods of up to 6 months when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk.

2.3 Polyarticular Juvenile Idiopathic Arthritis

Naproxen solid-oral dosage forms may not allow for the flexible dose titration needed in pediatric patients with polyarticular juvenile idiopathic arthritis. A liquid formulation may be more appropriate for weight-based dosing and due to the need for dose flexibility in children.

In pediatric patients, doses of 5 mg/kg/day produced plasma levels of naproxen similar to those seen in adults taking 500 mg of naproxen [see Clinical Pharmacology (12)]. The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses. Dosing with NAPROSYN Tablets is not appropriate for children weighing less than 50 kilograms.

2.4 Management of Pain, Primary Dysmenorrhea, and Acute Tendonitis and Bursitis

The recommended starting dose of ANAPROX DS (naproxen sodium) tablets is 550 mg followed by 550 mg every 12 hours or 275 mg (one half of a 550 mg tablet) every 6 to 8 hours as required. The initial total daily dose should not exceed 1375 mg (two and one-half tablets) of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. Because the sodium salt of naproxen is more rapidly absorbed, ANAPROX DS is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. NAPROSYN Tablets may also be used. The recommended starting dose of NAPROSYN Tablets is 500 mg followed by 250 mg (one half of a 500 mg NAPROSYN tablet) every 6-8 hours as required. The total daily dose should not exceed 1250 mg of naproxen.

EC-NAPROSYN is not recommended for initial treatment of acute pain because absorption of naproxen is delayed compared to other naproxen-containing products [see Clinical Pharmacology (12)].

2.5 Acute Gout

The recommended starting dose is 750 mg (one and one-half tablets) of NAPROSYN Tablets followed by 250 mg (one-half tablet) every 8 hours until the attack has subsided. ANAPROX DS may also be used at a starting dose of 825 mg (one and one-half tablets) followed by 275 mg (one-half tablet) every 8 hours. EC-NAPROSYN is not recommended because of the delay in absorption.
2.6 Non-Interchangeability with Other Formulations of Naproxen

Different dose strengths and formulations (e.g., tablets, suspension) of naproxen are not interchangeable. This difference should be taken into consideration when changing strengths or formulations.

3 DOSAGE FORMS AND STRENGTHS

NAPROSYN® (naproxen) tablets: 500 mg: yellow, capsule-shaped, engraved with NPR LE 500 on one side and scored on the other.

EC-NAPROSYN® (naproxen) delayed-release tablets: 375 mg: white, oval biconvex coated tablets imprinted with NPR EC 375 on one side.

EC-NAPROSYN® (naproxen) delayed-release tablets: 500 mg: white, oblong coated tablets imprinted with NPR EC 500 on one side.

ANAPROX® DS (naproxen sodium) tablets: 550 mg: dark blue, oblong-shaped, engraved with NPS 550 on one side and scored on both sides.

4 CONTRAINDICATIONS

NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS are contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to naproxen or any components of the drug product [see Warnings and Precautions (5.7, 5.9)]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [see Warnings and Precautions (5.7, 5.8)]
- In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as naproxen, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated
patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including naproxen, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see Drug Interactions (7)].

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including naproxen.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [see Drug Interactions (7)].
Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema
The Coxib and traditional NSAID Trialists’ Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of naproxen may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [see Drug Interactions (7)].

Avoid the use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Since each ANAPROX DS tablet contains 50 mg of sodium (about 2 mEq per each 500 mg of naproxen), this should be considered in patients whose overall intake of sodium must be severely restricted.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS in patients with advanced renal disease. The renal effects of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS [see Drug Interactions (7)]. Avoid the use of NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia
Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.7 Anaphylactic Reactions

Naproxen has been associated with anaphylactic reactions in patients with and without known hypersensitivity to naproxen and in patients with aspirin-sensitive asthma [see Contraindications (4) and Warnings and Precautions (5.8)].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs.
Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS are contraindicated in patients with this form of aspirin sensitivity [see Contraindications (4)]. When NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions
NSAIDs, including naproxen, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS at the first appearance of skin rash or any other sign of hypersensitivity. NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS are contraindicated in patients with previous serious skin reactions to NSAIDs [see Contraindications (4)].

5.10 Premature Closure of Fetal Ductus Arteriosus
Naproxen may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS, in pregnant women starting at 30 weeks of gestation (third trimester) [see Use in Specific Populations (8.1)].

5.11 Hematologic Toxicity
Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin and other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [see Drug Interactions (7)].

5.12 Masking of Inflammation and Fever
The pharmacological activity of NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.13 Long-Term Use and Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [see Warnings and Precautions (5.2, 5.3, 5.6)].

Patients with initial hemoglobin values of 10g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Cardiovascular Thrombotic Events [see Warnings and Precautions (5.1)]
- GI Bleeding, Ulceration, and Perforation [see Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Hypertension [see Warnings and Precautions (5.4)]
- Heart Failure and Edema [see Warnings and Precautions (5.5)]
- Renal Toxicity and Hyperkalemia [see Warnings and Precautions (5.6)]
• Anaphylactic Reactions [see Warnings and Precautions (5.7)]
• Serious Skin Reactions [see Warnings and Precautions (5.9)]
• Hematologic Toxicity [see Warnings and Precautions (5.11)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen.

In controlled clinical trials with about 80 pediatric patients and in well-monitored, open-label studies with about 400 pediatric patients with polyarticular juvenile idiopathic arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were greater, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

In patients taking naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients were:

Gastrointestinal (GI) Experiences, including: heartburn*, abdominal pain*, nausea*, constipation*, diarrhea, dyspepsia, stomatitis

Central Nervous System: headache*, dizziness*, drowsiness*, lightheadedness, vertigo

Dermatologic: pruritus (itching)*, skin eruptions*, ecchymoses*, sweating, purpura

Special Senses: tinnitus*, visual disturbances, hearing disturbances

Cardiovascular: edema*, palpitations

General: dyspnea*, thirst

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1% to 10% of patients.

Gastrointestinal (GI) Experiences, including: flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting

General: abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes

The following are additional adverse experiences reported in <1% of patients taking naproxen during clinical trials.

Gastrointestinal: pancreatitis, vomiting

Hepatobiliary: jaundice

Hemic and Lymphatic: melena, thrombocytopenia, agranulocytosis

Nervous System: inability to concentrate

Dermatologic: skin rashes

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of naproxen. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following are additional adverse experiences reported in <1% of patients taking naproxen during clinical trials and through postmarketing reports. Those adverse reactions observed through postmarketing reports are italicized.

**Body as a Whole:** anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)

**Cardiovascular:** congestive heart failure, vasculitis, hypertension, pulmonary edema

**Gastrointestinal:** inflammation, bleeding (sometimes fatal, particularly in the elderly), ulceration, perforation and obstruction of the upper or lower gastrointestinal tract. Esophagitis, stomatitis, hematemesis, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn’s disease).

**Hepatobiliary:** abnormal liver function tests, hepatitis (some cases have been fatal)

**Hemic and Lymphatic:** eosinophilia, leucopenia, granulocytopenia, hemolytic anemia, aplastic anemia

**Metabolic and Nutritional:** hyperglycemia, hypoglycemia

**Nervous System:** depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions

**Respiratory:** eosinophilic pneumonitis, asthma

**Dermatologic:** alopecia, urticaria, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematoses, bullous reactions, including Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

**Special Senses:** hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema

**Urogenital:** glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine

**Reproduction (female):** infertility

In patients taking NSAIDs, the following adverse experiences have also been reported in <1% of patients.

**Body as a Whole:** fever, infection, sepsis, anaphylactic reactions, appetite changes, death

**Cardiovascular:** hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction

**Gastrointestinal:** dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, cructation

**Hepatobiliary:** hepatitis, liver failure

**Hemic and Lymphatic:** rectal bleeding, lymphadenopathy, pancytopenia

**Metabolic and Nutritional:** weight changes

**Nervous System:** anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations

**Respiratory:** asthma, respiratory depression, pneumonia

**Dermatologic:** exfoliative dermatitis
7 DRUG INTERACTIONS
See Table 1 for clinically significant drug interactions with naproxen.

Table 1: Clinically Significant Drug Interactions with naproxen

<table>
<thead>
<tr>
<th>Drugs That Interfere with Hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact:</strong></td>
</tr>
<tr>
<td>• Naproxen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of naproxen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone.</td>
</tr>
<tr>
<td>• Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.</td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
</tr>
<tr>
<td>Monitor patients with concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [see Warnings and Precautions (5.4)].</td>
</tr>
</tbody>
</table>

**Aspirin**

| **Clinical Impact:**                |
| Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [see Warnings and Precautions (5.2)]. |
| **Intervention:**                   |
| Concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [see Warnings and Precautions (5.1)]. |
| NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS are not substitutes for low dose aspirin for cardiovascular protection. |

**ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers**

| **Clinical Impact:**                |
| • NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). |
| • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. |
| **Intervention:**                   |
| • During concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. |
| • During concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [see Warnings and Precautions (5.6)]. |
| • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter. |

**Diuretics**
<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.</td>
<td>During concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see Warnings and Precautions (5.6)].</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Intervention</td>
</tr>
<tr>
<td>The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.</td>
<td>During concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and digoxin, monitor serum digoxin levels.</td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Intervention</td>
</tr>
<tr>
<td>NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.</td>
<td>During concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and lithium, monitor patients for signs of lithium toxicity.</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Intervention</td>
</tr>
<tr>
<td>Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).</td>
<td>During concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and methotrexate, monitor patients for methotrexate toxicity.</td>
</tr>
<tr>
<td><strong>Cyclosporine</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Intervention</td>
</tr>
<tr>
<td>Concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and cyclosporine may increase cyclosporine’s nephrotoxicity.</td>
<td>During concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and cyclosporine, monitor patients for signs of worsening renal function.</td>
</tr>
<tr>
<td><strong>NSAIDs and Salicylates</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Intervention</td>
</tr>
<tr>
<td>Concomitant use of naproxen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [see Warnings and Precautions (5.2)].</td>
<td>The concomitant use of naproxen with other NSAIDs or salicylates is not recommended.</td>
</tr>
<tr>
<td><strong>Pemetrexed</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Intervention</td>
</tr>
<tr>
<td>Concomitant use of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).</td>
<td>During concomitant use of NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.</td>
</tr>
<tr>
<td><strong>Antacids and Sucralfate</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Clinical Impact:
Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.

### Intervention:
Concomitant administration of antacids such as magnesium oxide or aluminum hydroxide, and sucralfate with NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS is not recommended.

### Cholestryramine

#### Clinical Impact:
Concomitant administration of cholestryramine can delay the absorption of naproxen.

#### Intervention:
Concomitant administration of cholestryramine with NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS is not recommended.

### Probencid

#### Clinical Impact:
Probencid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

#### Intervention:
Patients simultaneously receiving NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and probencid should be observed for adjustment of dose if required.

### Other albumin-bound drugs

#### Clinical Impact:
Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin.

#### Intervention:
Patients simultaneously receiving NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

## Drug/Laboratory Test Interactions

### Bleeding times

#### Clinical Impact:
Naproxen may decrease platelet aggregation and prolong bleeding time.

#### Intervention:
This effect should be kept in mind when bleeding times are determined.

### Porter-Silber test

#### Clinical Impact:
The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay.

#### Intervention:
Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artificially altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

### Urinary assays of 5-hydroxy indoleacetic acid (5HIAA)

#### Clinical Impact:
Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

#### Intervention:
This effect should be kept in mind when urinary 5-hydroxy indoleacetic acid is determined.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Use of NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS, in pregnant women starting at 30 weeks of gestation (third trimester).
There are no adequate and well-controlled studies of NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies in rats, rabbits, and mice no evidence of teratogenicity or fetal harm when naproxen was administered during the period of organogenesis at doses 0.13, 0.26, and 0.6 times the maximum recommended human daily dose of 1500 mg/day, respectively [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS during labor or delivery. In animal studies, NSAIDS, including naproxen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor, there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly starting at 30-weeks of gestation, or third trimester) should be avoided.

Animal data

Reproduction studies have been performed in rats at 20 mg/kg/day (0.13 times the maximum recommended human daily dose of 1500 mg/day based on body surface area comparison), rabbits at 20 mg/kg/day (0.26 times the maximum recommended human daily dose, based on body surface area comparison), and mice at 170 mg/kg/day (0.6 times the maximum recommended human daily dose based on body surface area comparison) with no evidence of impaired fertility or harm to the fetus due to the drug. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen, resulted in increased pre- and post-implantation loss.

8.2 Lactation

Risk Summary

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS and any potential adverse effects on the breastfed infant from the NAPROSYN Tablets, EC-NAPROSYN, or ANAPROX DS or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for polyarticular juvenile idiopathic arthritis are based on well-controlled studies [see Dosage and Administration (2)]. There are no adequate effectiveness or dose-response data for other pediatric conditions, but the
experience in polyarticular juvenile idiopathic arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg as naproxen suspension, with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

8.5 Geriatric Use
The hepatic and renal tolerability of long-term naproxen administration was studied in two double-blind clinical trials involving 586 patients. Of the patients studied, 98 patients were age 65 and older and 10 of the 98 patients were age 75 and older. NAPROXEN was administered at doses of 375 mg twice daily or 750 mg twice daily for up to 6 months. Transient abnormalities of laboratory tests assessing hepatic and renal function were noted in some patients, although there were no differences noted in the occurrence of abnormal values among different age groups.

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.13)].

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of nonsteroidal anti-inflammatory drugs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population [see Warnings and Precautions (5.2)].

Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Clinical Pharmacology (12.3)]. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs [see Warnings and Precautions (5.6)].

8.6 Hepatic Impairment
Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose [see Clinical Pharmacology (12.3)].

8.7 Renal Impairment
Naproxen-containing products are not recommended for use in patients with moderate to severe renal impairment (creatinine clearance <30 mL/min) [see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)].

10 OVERDOSAGE
Symptoms following acute NSAID overdoses have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [see Warnings and Precautions (5.1, 5.2)]. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening [see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)].

Manage patients with symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdose (5 to 10 times the recommended dosage). Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdose treatment contact a poison control center (1-800-222-1222).
11 DESCRIPTION

NAPROSYN (naproxen) tablets, EC-NAPROSYN (naproxen) delayed-release tablets and ANAPROX DS (naproxen sodium) tablets are nonsteroidal anti-inflammatory drugs available as follows: NAPROSYN tablets are available as yellow tablets containing 500 mg of naproxen for oral administration.

EC-NAPROSYN delayed-release tablets are available as enteric-coated white tablets containing 375 mg of naproxen or 500 mg of naproxen for oral administration.

ANAPROX DS tablets are available as dark blue tablets containing 550 mg of naproxen sodium for oral administration.

Naproxen is a propionic acid derivative related to the arylacetic acid group of nonsteroidal anti-inflammatory drugs. The chemical names for naproxen and naproxen sodium are (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid and (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid, sodium salt, respectively. Naproxen has a molecular weight of 230.26 and a molecular formula of C₁₄H₁₄O₃. Naproxen sodium has a molecular weight of 252.23 and a molecular formula of C₁₄H₁₃NaO₃. Naproxen and naproxen sodium have the following structures, respectively:

Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8. Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

The inactive ingredients in NAPROSYN tablets include: croscarmellose sodium, iron oxides, povidone and magnesium stearate.

The inactive ingredients in EC-NAPROSYN delayed release tablets include: croscarmellose sodium, povidone and magnesium stearate. The enteric coating dispersion contains methacrylic acid copolymer, talc, triethyl citrate, sodium hydroxide and purified water. The imprinting on the tablets is black ink. The dissolution of this enteric-coated naproxen tablet is pH dependent with rapid dissolution above pH 6. There is no dissolution below pH 4.

The inactive ingredients in ANAPROX DS tablets include: magnesium stearate, microcrystalline cellulose, povidone and talc. The coating suspension may contain hydroxypropyl methylcellulose 2910, Opaspray K-1-4227, polyethylene glycol 8000 or Opadry YS-1-4216.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Naproxen has analgesic, anti-inflammatory, and antipyretic properties. ANAPROX DS (naproxen sodium) has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic.

The mechanism of action of naproxen, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Naproxen is a potent inhibitor of prostaglandin synthesis in vitro. Naproxen concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because naproxen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacokinetics

Naproxen and naproxen sodium are rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. The different dosage forms of NAPROSYN are bioequivalent in terms of extent of absorption (AUC) and peak concentration (Cₘₐₓ); however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical form of naproxen used and its formulation. Even with the observed
differences in pattern of absorption, the elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negligible role in the attainment of steady-state plasma levels.

**Absorption**

**NAPROSYN Tablets/ANAPROX DS:**
After administration of NAPROSYN Tablets, peak plasma levels are attained in 2 to 4 hours. After oral administration of ANAPROX DS, peak plasma levels are attained in 1 to 2 hours. The difference in rates between the two products is due to the increased aqueous solubility of the sodium salt of naproxen used in ANAPROX DS.

**EC-NAPROSYN:**
EC-NAPROSYN is designed with a pH-sensitive coating to provide a barrier to disintegration in the acidic environment of the stomach and to lose integrity in the more neutral environment of the small intestine. The enteric polymer coating selected for EC-NAPROSYN dissolves above pH 6. When EC-NAPROSYN was given to fasted subjects, peak plasma levels were attained about 4 to 6 hours following the first dose (range: 2 to 12 hours). An in vivo study in man using radiolabeled EC-NAPROSYN tablets demonstrated that EC-NAPROSYN dissolves primarily in the small intestine rather than in the stomach, so the absorption of the drug is delayed until the stomach is emptied.

When EC-NAPROSYN and NAPROSYN Tablets were given to fasted subjects (n=24) in a crossover study following 1 week of dosing, differences in time to peak plasma levels (T<sub>max</sub>) were observed, but there were no differences in total absorption as measured by C<sub>max</sub> and AUC:

<table>
<thead>
<tr>
<th></th>
<th>EC-NAPROSYN*</th>
<th>NAPROSYN*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>94.9 (18%)</td>
<td>97.4 (13%)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hours)</td>
<td>4 (39%)</td>
<td>1.9 (61%)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12 hr&lt;/sub&gt; (µg·hr/mL)</td>
<td>845 (20%)</td>
<td>767 (15%)</td>
</tr>
</tbody>
</table>

*Mean value (coefficient of variation)

**Antacid Effects**

When EC-NAPROSYN was given as a single dose with antacid (54 mEq buffering capacity), the peak plasma levels of naproxen were unchanged, but the time to peak was reduced (mean T<sub>max</sub> fasted 5.6 hours, mean T<sub>max</sub> with antacid 5 hours), although not significantly [see Drug Interactions (7)].

**Food Effects**

When EC-NAPROSYN was given as a single dose with food, peak plasma levels in most subjects were achieved in about 12 hours (range: 4 to 24 hours). Residence time in the small intestine until disintegration was independent of food intake. The presence of food prolonged the time the tablets remained in the stomach, time to first detectable serum naproxen levels, and time to maximal naproxen levels (T<sub>max</sub>), but did not affect peak naproxen levels (C<sub>max</sub>).

**Distribution**

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C<sub>ss</sub> 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma [see Use in Specific Populations(8.2)].

**Elimination**

**Metabolism**

Naproxen is extensively metabolized in the liver to 6-O-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-O-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

**Excretion**
The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (<1%), 6-O-desmethyl naproxen (<1%) or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen’s metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen clearance from the plasma. Small amounts, 3% or less of the administered dose, are excreted in the feces. In patients with renal failure metabolites may accumulate [see Warnings and Precautions (5.6)].

Specific Populations

**Pediatric:**
In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension [see Dosage and Administration (2)] were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen suspension or tablets in pediatric patients.

**Geriatric:**
Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is <1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects.

**Hepatic Impairment:**
Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased.

**Renal Impairment:**
Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment.

**Drug Interaction Studies**

**Aspirin:** When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 1 for clinically significant drug interactions of NSAIDs with aspirin [see Drug Interactions (7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis**
A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16, and 24 mg/kg/day (0.05, 0.1, and 0.16 times the maximum recommended human daily dose [MRHD] of 1500 mg/day based on a body surface area comparison). No evidence of tumorigenicity was found.

**Mutagenesis**
Naproxen tested positive in the in vivo sister chromatid exchange assay for but was not mutagenic in the in vitro bacterial reverse mutation assay (Ames test).

**Impairment of Fertility**
Male rats were treated with 2, 5, 10, and 20 mg/kg naproxen by oral gavage for 60 days prior to mating and female rats were treated with the same doses for 14 days prior to mating and for the first 7 days of pregnancy. There were no adverse effects on fertility noted (up to 0.13 times the MRDH based on body surface area).

14 CLINICAL STUDIES

Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute gout. Improvement in patients treated for rheumatoid arthritis was
demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time. Generally, response to naproxen has not been found to be dependent on age, sex, severity or duration of rheumatoid arthritis.

In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In a clinical trial comparing standard formulations of naproxen 375 mg twice a day (750 mg a day) vs 750 mg twice a day (1500 mg/day), 9 patients in the 750 mg group terminated prematurely because of adverse events. Nineteen patients in the 1500 mg group terminated prematurely because of adverse events. Most of these adverse events were gastrointestinal events.

In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and polyarticular juvenile idiopathic arthritis, naproxen has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less in naproxen-treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

In patients with acute gout, a favorable response to naproxen was shown by significant clearing of inflammatory changes (e.g., decrease in swelling, heat) within 24 to 48 hours, as well as by relief of pain and tenderness.

Naproxen has been studied in patients with mild to moderate pain secondary to postoperative, orthopedic, postpartum episiotomy and uterine contraction pain and dysmenorrhea. Onset of pain relief can begin within 1 hour in patients taking naproxen and within 30 minutes in patients taking naproxen sodium. Analgesic effect was shown by such measures as reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time to remission. The analgesic effect has been found to last for up to 12 hours.

Naproxen may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids, it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether naproxen has a “steroid-sparing” effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs, the combination may result in higher frequency of adverse events than demonstrated for either product alone.

In $^{51}$Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of naproxen as 1000 mg of NAPROSYN (naproxen) or 1100 mg of ANAPROX DS (naproxen sodium) has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

Three 6-week, double-blind, multicenter studies with EC-NAPROSYN (naproxen) (375 or 500 mg twice a day, n=385) and NAPROSYN (375 or 500 mg twice a day, n=279) were conducted comparing EC-NAPROSYN with NAPROSYN, including 355 rheumatoid arthritis and osteoarthritis patients who had a recent history of NSAID-related GI symptoms. These studies indicated that EC-NAPROSYN and NAPROSYN showed no significant differences in efficacy or safety and had similar prevalence of minor GI complaints. Individual patients, however, may find one formulation preferable to the other.

Five hundred and fifty-three patients received EC-NAPROSYN during long-term open-label trials (mean length of treatment was 159 days). The rates for clinically-diagnosed peptic ulcers and GI bleeds were similar to what has been historically reported for long-term NSAID use.

16 HOW SUPPLIED/STORAGE AND HANDLING

NAPROSYN (naproxen) tablets 500 mg: yellow, capsule-shaped tablets, engraved with NPR LE 500 on one side and scored on the other. Packaged in light-resistant bottles of 100. Supplied as:

NDC 69437-316-01 100’s (bottle)

Store at 15°C to 30°C (59°F to 86°F) in well-closed containers; dispense in light-resistant containers.
EC-NAPROSYN (naproxen) delayed-release tablets 375 mg: white, oval biconvex coated tablets imprinted with NPR EC 375 on one side. Packaged in light-resistant bottles of 100. Supplied as:

NDC 69437-415-01 100’s (bottle)

500 mg: white, oblong coated tablets imprinted with NPR EC 500 on one side. Packaged in light-resistant bottles of 100. Supplied as:

NDC 69437-416-01 100’s (bottle)

Store at 15°C to 30°C (59°F to 86°F) in well-closed containers; dispense in light-resistant containers.

ANAPROX DS (naproxen sodium) Tablets 550 mg: dark blue, oblong-shaped tablets, engraved with NPS 550 on one side and scored on both sides. Packaged in bottles of 100. Supplied as:

NDC 69437-203-01 100’s (bottle)

Store at 15°C to 30°C (59°F to 86°F) in well-closed containers.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see Warnings and Precautions (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [see Warnings and Precautions (5.2)].

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS and seek immediate medical therapy [see Warnings and Precautions (5.3)].

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see Warnings and Precautions (5.5)].

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [see Contraindications (4) and Warnings and Precautions (5.7)].

Serious Skin Reactions

Advise patients to stop NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [see Warnings and Precautions (5.9)].

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS, may be associated with a reversible delay in ovulation (see Use in Specific Populations (8.3)).
Fetal Toxicity
Inform pregnant women to avoid use of NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus [see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)].

Avoid Concomitant Use of NSAIDs
Inform patients that the concomitant use of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see Warnings and Precautions (5.2) and Drug Interactions (7)]. Alert patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concomitantly with NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS until they talk to their healthcare provider [see Drug Interactions (7)].

Manufactured for:
Atnahs Pharma, Miles Gray Road, Basildon, Essex, SS14 3FR, United Kingdom

Distributed by:
Canton Laboratories, LLC., Alpharetta, GA 30004-5945, United States
What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

• Increased risk of a heart attack or stroke that can lead to death. This risk may happen early in treatment and may increase:
  o with increasing doses of NSAIDs
  o with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft (CABG).”

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

• Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:
  o anytime during use
  o without warning symptoms
  o that may cause death

The risk of getting an ulcer or bleeding increases with:
  o past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  o taking medicines called “corticosteroids”, “anticoagulants”, “SSRIs”, or “SNRIs”
  o increasing doses of NSAIDs
  o longer use of NSAIDs
  o smoking
  o drinking alcohol

The risk of getting an ulcer or bleeding increases with:
  o older age
  o poor health
  o advanced liver disease
  o bleeding problems

NSAIDs should only be used:
  o exactly as prescribed
  o at the lowest dose possible for your treatment
  o for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:
  • if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
  • right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:
  • have liver or kidney problems
  • have high blood pressure
  • have asthma
  • are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 29 weeks of pregnancy.
  • are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your healthcare provider first.

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)”

• new or worse high blood pressure
• heart failure
• liver problems including liver failure
• kidney problems including kidney failure
• low red blood cells (anemia)
• life-threatening skin reactions
• life-threatening allergic reactions

• Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:
  • shortness of breath or trouble breathing
  • chest pain
  • weakness in one part or side of your body
  • slurred speech
  • swelling of the face or throat
Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Manufactured for: Atnahs Pharma, Miles Gray Road, Basildon, Essex, SS14 3FR, United Kingdom
Distributed by: Canton Laboratories, LLC, Alpharetta, GA 30004-5945, United States
For more information, call 1-844-302-5227.
IBUPROFEN- ibuprofen tablet
Amneal Pharmaceuticals LLC

---------

Ibuprofen Tablets, USP
(400 mg, 600 mg and 800 mg)
Rx Only

Cardiovascular Thrombotic Events
- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [see WARNINGS and PRECAUTIONS].
- Ibuprofen Tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see CONTRAINDICATIONS and WARNINGS].

Gastrointestinal Risk
- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events [see WARNINGS].

DESCRIPTION
Ibuprofen Tablets, USP contain the active ingredient ibuprofen, which is (±)-2-(p-isobutylphenyl) propionic acid. Ibuprofen is a white powder with a melting point of 74° to 77° C and is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone.

The structural formula is represented below:

![Chemical Structure of Ibuprofen](image)

Ibuprofen Tablets, USP, a nonsteroidal anti-inflammatory drug (NSAID), is available in 400 mg, 600 mg, and 800 mg tablets for oral administration. Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, pregelatinized starch, talc, stearic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY
Ibuprofen tablets contain ibuprofen which possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin
In clinical studies in patients with rheumatoid arthritis and osteoarthritis, ibuprofen tablets have been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder gastrointestinal side effects [see ADVERSE REACTIONS]. Ibuprofen tablets may be well tolerated in some patients who have had gastrointestinal side effects with aspirin, but these patients when treated with ibuprofen tablets should be carefully followed for signs and symptoms of gastrointestinal ulceration and bleeding. Although it is not definitely known whether ibuprofen tablets causes less peptic ulceration than aspirin, in one study involving 885 patients with rheumatoid arthritis treated for up to one year, there were no reports of gastric ulceration with ibuprofen tablets whereas frank ulceration was reported in 13 patients in the aspirin group (statistically significant p <0.001). Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin. Studies using $^{51}$Cr-tagged red cells indicate that fecal blood loss associated with ibuprofen tablets in doses up to 2400 mg daily did not exceed the normal range, and was significantly less than that seen in aspirin-treated patients.

In clinical studies in patients with rheumatoid arthritis, ibuprofen tablets have been shown to be comparable to indomethacin in controlling the signs and symptoms of disease activity and to be associated with a statistically significant reduction of the milder gastrointestinal [see ADVERSE REACTIONS] and CNS side effects.

Ibuprofen tablets may be used in combination with gold salts and/or corticosteroids.

Controlled studies have demonstrated that ibuprofen tablets are a more effective analgesic than propoxyphene for the relief of episiotomy pain, pain following dental extraction procedures, and for the relief of the symptoms of primary dysmenorrhea.

In patients with primary dysmenorrhea, ibuprofen tablets have been shown to reduce elevated levels of prostaglandin activity in the menstrual fluid and to reduce resting and active intrauterine pressure, as well as the frequency of uterine contractions. The probable mechanism of action is to inhibit prostaglandin synthesis rather than simply to provide analgesia.

The ibuprofen in ibuprofen tablets is rapidly absorbed. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under the serum drug concentration vs time curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction.

The administration of ibuprofen tablets either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. When ibuprofen tablets are administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption. The bioavailability of the drug is minimally altered by the presence of food. A bioavailability study has shown that there was no interference with the absorption of ibuprofen when ibuprofen tablets were given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide. Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours.

Studies have shown that following ingestion of the drug, 45% to 79% of the dose was recovered in the urine within 24 hours as metabolite A (25%), (+)-2-[(2-hydroxymethyl-propyl) phenyl] propionic acid and metabolite B (37%), (+)-2-[p-(2-carboxypropyl)phenyl] propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

**INDICATIONS AND USAGE**

Carefully consider the potential benefits and risks of Ibuprofen Tablets and other treatment options.
before deciding to use Ibuprofen Tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [see WARNINGS].

Ibuprofen Tablets are indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Ibuprofen Tablets are indicated for relief of mild to moderate pain.

Ibuprofen Tablets are also indicated for the treatment of primary dysmenorrhea.

Controlled clinical trials to establish the safety and effectiveness of Ibuprofen Tablets in children have not been conducted.

**CONTRAINDICATIONS**

Ibuprofen tablets are contraindicated in patients with known hypersensitivity to ibuprofen.

Ibuprofen tablets should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.

Severe, rarely fatal, anaphylactoid-like reactions to NSAIDs have been reported in such patients [see WARNINGS, Anaphylactoid Reactions, and PRECAUTIONS, Preexisting Asthma].

In the setting of coronary artery bypass graft (CABG) surgery [see WARNINGS].

**WARNINGS**

**CARDIOVASCULAR EFFECTS**

**Cardiovascular Thrombotic Events**

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as ibuprofen, increases the risk of serious gastrointestinal (GI) events [see WARNINGS].

**Status Post Coronary Artery Bypass Graft (CABG) Surgery**

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see CONTRAINDICATIONS].

**Post-MI Patients**

Observational studies conducted in the Danish National Registry have demonstrated that patients treated...
with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of ibuprofen tablets in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ibuprofen tablets are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

**Hypertension**

NSAIDs including ibuprofen tablets can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including ibuprofen tablets should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

**Heart Failure and Edema**

The Coxib and traditional NSAID Trialists’ Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of Ibuprofen may blunt the CV effects of several therapeutic agents used to treat these medical conditions [e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)] [see DRUG INTERACTIONS].

Avoid the use of ibuprofen tablets in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ibuprofen tablets are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

**Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation**

NSAIDs, including ibuprofen tablets can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients treated with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population. To minimize the potential risk for an adverse GI event in patients treated with a NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional
evaluation and treatment if a serious GI event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of ibuprofen tablets in patients with advanced renal disease. Therefore, treatment with ibuprofen tablets is not recommended in these patients with advanced renal disease. If ibuprofen tablets therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ibuprofen tablets. Ibuprofen tablets should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs [see CONTRAINDICATIONS and PRECAUTIONS, Preexisting Asthma].

Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including ibuprofen tablets can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, ibuprofen tablets should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

Ibuprofen tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of ibuprofen tablets in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including ibuprofen tablets. These laboratory abnormalities may progress, may remain unchanged, or
may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice, fulminant hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes have been reported. A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ibuprofen tablets. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ibuprofen tablets should be discontinued.

**Hematological effects**

Anemia is sometimes seen in patients receiving NSAIDs, including ibuprofen tablets. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including ibuprofen tablets should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

In two postmarketing clinical studies the incidence of a decreased hemoglobin level was greater than previously reported. Decrease in hemoglobin of 1 gram or more was observed in 17.1% of 193 patients on 1600 mg ibuprofen daily (osteoarthritis), and in 22.8% of 189 patients taking 2400 mg of ibuprofen daily (rheumatoid arthritis). Positive stool occult blood tests and elevated serum creatinine levels were also observed in these studies.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible.

Patients receiving ibuprofen tablets who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants should be carefully monitored.

**Preexisting asthma**

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, ibuprofen tablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

**Ophthalmological effects**

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving ibuprofen tablets, the drug should be discontinued, and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

**Aseptic Meningitis**

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen tablets, the possibility of its being related to ibuprofen tablets should be considered.

**Information for Patients**

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy.
Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

- **Cardiovascular Thrombotic Events**
  Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see WARNINGS].

- Ibuprofen tablets, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up [see WARNINGS, Gastrointestinal Effects - Risk of Ulceration, Bleeding and Perforation].

- Ibuprofen tablets, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS and TEN, which may result in hospitalization and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms.

- Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

- **Heart Failure And Edema**
  Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see WARNINGS].

- Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

- Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help [see WARNINGS].

- In late pregnancy, as with other NSAIDs, ibuprofen tablets should be avoided because it may cause premature closure of the ductus arteriosus.

**Laboratory Tests**

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash etc.), or abnormal liver tests persist or worsen, ibuprofen tablets should be discontinued.

**Drug Interactions**

**ACE-inhibitors:**

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

**Aspirin**

When ibuprofen tablets are administered with aspirin, its protein binding is reduced, although the clearance of free ibuprofen tablets is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of ibuprofen and aspirin is not generally recommended because of the potential for increased adverse effects.
**Diuretics**

Clinical studies, as well as post marketing observations, have shown that ibuprofen tablets can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure [see WARNINGS, Renal Effects], as well as to assure diuretic efficacy.

**Lithium**

Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration.

This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. (Read circulars for lithium preparation before use of such concurrent therapy.)

**Methotrexate**

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

**Warfarin-type anticoagulants**

Several short-term controlled studies failed to show that ibuprofen tablets significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. However, because bleeding has been reported when ibuprofen tablets and other NSAIDs have been administered to patients on coumarin-type anticoagulants, the physician should be cautious when administering ibuprofen tablets to patients on anticoagulants. The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that the users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

**H-2 Antagonists**

In studies with human volunteers, co-administration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

**Pregnancy**

**Teratogenic effects: Pregnancy Category C**

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Ibuprofen should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic effects**

Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided.

**Labor and Delivery**

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of ibuprofen tablets on labor and delivery in pregnant women are unknown.

**Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ibuprofen tablets,
a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**
Safety and effectiveness of ibuprofen tablets in pediatric patients have not been established.

**Geriatric Use**
As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

**ADVERSE REACTIONS**
The most frequent type of adverse reaction occurring with ibuprofen tablets is gastrointestinal. In controlled clinical trials the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

In controlled studies when ibuprofen tablets were compared to aspirin and indomethacin in equally effective doses, the overall incidence of gastrointestinal complaints was about half that seen in either the aspirin- or indomethacin-treated patients.

Adverse reactions observed during controlled clinical trials at an incidence greater than 1% are listed in the table. Those reactions listed in Column one encompass observations in approximately 3,000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.

Still other reactions occurring less frequently than 1 in 100 were reported in controlled clinical trials and from marketing experience. These reactions have been divided into two categories: Column two of the table lists reactions with therapy with ibuprofen tablets where the probability of a causal relationship exists: for the reactions in Column three, a causal relationship with ibuprofen tablets has not been established.

Reported side effects were higher at doses of 3200 mg/day than at doses of 2400 mg or less per day in clinical trials of patients with rheumatoid arthritis. The increases in incidence were slight and still within the ranges reported in the table.

<table>
<thead>
<tr>
<th>Incidence Greater Than 1% (but less than 3%)</th>
<th>Precise Incidence Unknown (but less than 1%)</th>
<th>Precise Incidence Unknown (but less than 1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable Causal Relationship</td>
<td>Probable Causal Relationship**</td>
<td>Causal Relationship Unknown**</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td>Gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; pancreatitis</td>
<td>Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri</td>
</tr>
<tr>
<td>Nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence)</td>
<td>Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; pancreatitis</td>
<td>Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri</td>
</tr>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
<td>Depression, insomnia, confusion, emotional liability, somnolence, aseptic meningitis with fever and coma [see PRECAUTIONS]</td>
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<tr>
<td>Dizziness*, headache, nervousness</td>
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<tr>
<td><strong>DERMATOLOGIC</strong></td>
<td>Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia</td>
<td>Toxic epidermal necrolysis, photoallergic skin reactions</td>
</tr>
<tr>
<td>Rash* (including maculopapular type), pruritus</td>
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April 24 and 25, 2018
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<th>SPECIAL SENSES</th>
<th>Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) [see PRECAUTIONS]</th>
<th>Conjunctivitis, diplopia, optic neuritis, cataracts</th>
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<tr>
<td>Tinnitus</td>
<td>Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit [see PRECAUTIONS]</td>
<td>Bleeding episodes (e.g., epistaxis, menorrhagia)</td>
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<thead>
<tr>
<th>HEMATOLOGIC</th>
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<td></td>
<td>Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit [see PRECAUTIONS]</td>
<td>Bleeding episodes (e.g., epistaxis, menorrhagia)</td>
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<thead>
<tr>
<th>METABOLIC/ENDOCRINE</th>
<th>Decreased appetite</th>
<th>Gynecomastia, hypoglycemic reaction, acidosis</th>
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<tr>
<th>CARDIOVASCULAR</th>
<th>Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations</th>
<th>Arrhythmias (sinus tachycardia, sinus bradycardia)</th>
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</thead>
<tbody>
<tr>
<td>Edema, fluid retention (generally responds promptly to drug discontinuation) [see PRECAUTIONS]</td>
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<table>
<thead>
<tr>
<th>ALLERGIC</th>
<th>Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm [see CONTRAINDICATIONS]</th>
<th>Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema</th>
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<th>Acute renal failure [see PRECAUTIONS], decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria</th>
<th>Renal papillary necrosis</th>
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<tr>
<th>MISCELLANEOUS</th>
<th>Dry eyes and mouth, gingival ulcer, rhinitis tests</th>
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* Reactions occurring in 3% to 9% of patients treated with ibuprofen tablets. (Those reactions occurring in less than 3% of the patients are unmarked.)

** Reactions are classified under “Probable Causal Relationship (PCR)” if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under “Causal Relationship Unknown” if seven or more events have been reported but the criteria for PCR have not been met.

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

OVERDOSAGE

Approximately 1½ hours after the reported ingestion of from 7 to 10 ibuprofen tablets (400 mg), a 19-month old child weighing 12 kg was seen in the hospital emergency room, apneic and cyanotic, responding only to painful stimuli. This type of stimulus, however, was sufficient to induce respiration. Oxygen and parenteral fluids were given; a greenish-yellow fluid was aspirated from the stomach with no evidence to indicate the presence of ibuprofen. Two hours after ingestion the child's condition seemed stable; she still responded only to painful stimuli and continued to have periods of apnea lasting from 5 to 10 seconds. She was admitted to intensive care and sodium bicarbonate was administered as well as infusions of dextrose and normal saline. By four hours post-ingestion she could be aroused easily, sit by herself and respond to spoken commands. Blood level of ibuprofen was 102.9 mcg/mL approximately 8½ hours after accidental ingestion. At 12 hours she appeared to be completely recovered. In two other reported cases where children (each weighing approximately 10 kg) accidentally, acutely ingested approximately 120 mg/kg, there were no signs of acute intoxication or
late sequelae. Blood level in one child 90 minutes after ingestion was 700 mcg/mL - about 10 times the peak levels seen in absorption-excretion studies.

A 19-year old male who had taken 8,000 mg of ibuprofen over a period of a few hours complained of dizziness, and nystagmus was noted. After hospitalization, parenteral hydration and three days bed rest, he recovered with no reported sequelae.

In cases of acute overdosage, the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Because the drug is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen tablets.

**DOSAGE AND ADMINISTRATION**

Carefully consider the potential benefits and risks of ibuprofen tablets and other treatment options before deciding to use ibuprofen tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [see WARNINGS].

After observing the response to initial therapy with ibuprofen tablets, the dose and frequency should be adjusted to suit an individual patient's needs.

Do not exceed 3200 mg total daily dose. If gastrointestinal complaints occur, administer ibuprofen tablets with meals or milk.

**Rheumatoid arthritis and osteoarthritis, including flare-ups of chronic disease:**

*Suggested Dosage:* 1200 mg to 3200 mg daily (300 mg qid; 400 mg, 600 mg or 800 mg tid or qid). Individual patients may show a better response to 3200 mg daily, as compared with 2400 mg, although in well-controlled clinical trials patients on 3200 mg did not show a better mean response in terms of efficacy.

Therefore, when treating patients with 3200 mg/day, the physician should observe sufficient increased clinical benefits to offset potential increased risk.

The dose should be tailored to each patient, and may be lowered or raised depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.

In general, patients with rheumatoid arthritis seem to require higher doses of ibuprofen tablets than do patients with osteoarthritis.

The smallest dose of ibuprofen tablets that yields acceptable control should be employed. A linear blood level dose-response relationship exists with single doses up to 800 mg [See CLINICAL PHARMACOLOGY for effects of food on rate of absorption].

The availability of four tablet strengths facilitates dosage adjustment.

*In chronic conditions,* a therapeutic response to therapy with ibuprofen tablets is sometimes seen in a few days to a week but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

**Mild to moderate pain:** 400 mg every 4 to 6 hours as necessary for relief of pain.

In controlled analgesic clinical trials, doses of ibuprofen tablets greater than 400 mg were no more effective than the 400 mg dose.

**Dysmenorrhea:** For the treatment of dysmenorrhea, beginning with the earliest onset of such pain, ibuprofen tablets should be given in a dose of 400 mg every 4 hours as necessary for the relief of pain.
Ibuprofen Tablets, USP are available in the following strengths, colors and sizes:

**400 mg** white, round, biconvex, aqueous film-coated tablets, debossed "IP 464" on obverse and plain on reverse. They are available as follows:

- Bottles of 30: NDC 65162-464-03
- Bottles of 60: NDC 65162-464-06
- Bottles of 90: NDC 65162-464-09
- Bottles of 100: NDC 65162-464-10
- Bottles of 500: NDC 65162-464-50

**600 mg** white, oval-shaped, biconvex, aqueous film-coated tablets, debossed "IP 465" on obverse and plain on reverse. They are available as follows:

- Bottles of 30: NDC 65162-465-03
- Bottles of 50: NDC 65162-465-05
- Bottles of 60: NDC 65162-465-06
- Bottles of 90: NDC 65162-465-09
- Bottles of 100: NDC 65162-465-10
- Bottles of 500: NDC 65162-465-50

**800 mg** white, capsule-shaped, biconvex, aqueous film-coated tablets, debossed "IP 466" on obverse and plain on reverse. They are available as follows:

- Bottles of 30: NDC 65162-466-03
- Bottles of 50: NDC 65162-466-05
- Bottles of 60: NDC 65162-466-06
- Bottles of 90: NDC 65162-466-09
- Bottles of 100: NDC 65162-466-10
- Bottles of 500: NDC 65162-466-50

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Avoid excessive heat 40°C (104°F). Dispense in a tight, light-resistant container as defined in the USP.

Rx Only

Manufactured by:

**Amneal Pharmaceuticals Pvt. Ltd.**

Oral Solid Dosage Unit

Ahmedabad 382213, INDIA

Distributed by:

**Amneal Pharmaceuticals LLC**

Bridgewater, NJ 08807

Rev. 08-2017-02
What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:
- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft (CABG).”

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:
- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called “corticosteroids”, “anticoagulants”, “SSRIs”, or “SNRIs”
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

NSAIDs should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?
NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?
Do not take NSAIDs:
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:
- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 29 weeks of pregnancy.
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your healthcare provider first.

What are the possible side effects of NSAIDs?
NSAIDs can cause serious side effects, including:
See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?”
- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting and dizziness.

Get emergency help right away if you get any of the following symptoms:
- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:
- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
• there is blood in your bowel movement or it is black and sticky like tar
• unusual weight gain
• skin rash or blisters with fever
• swelling of the arms, legs, hands, and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA1088.

Other information about NSAIDs
• Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
• Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

For more information, go to www.amneal.com or call 1-877-835-5472.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Amneal Pharmaceuticals Pvt. Ltd.
Oral Solid Dosage Unit
Ahmedabad 382213, INDIA

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807
Rev. 08-2017-02

PRINCIPAL DISPLAY PANEL
<table>
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<tr>
<th>IBUPROFEN</th>
<th>ibuprofen tablet</th>
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### Product Information

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### Active Ingredient/Active Moiety

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<th>Page 258</th>
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IBUPROFEN

ibuprofen tablet

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**IBUPROFEN**

ibuprofen tablet

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Active Ingredient/Active Moiety

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<th>Ingredient Name</th>
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Product Characteristics

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</table>
APPENDIX 1. Example Adult Ibuprofen Drug Facts Label

USES
- temporarily relieves minor aches and pains due to:
  - headache
  - toothache
  - backache
  - menstrual cramps
  - the common cold
  - muscular aches
  - minor pain of arthritis
- temporarily reduces fever

WARNINGS

Allergy alert:
Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning:
This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you
- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Heart attack and stroke warning
NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

Do not use
- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery
Ask a doctor before use if
- stomach bleeding warning applies to you
- you have problems or serious side effects from taking pain relievers or fever reducers
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
- you are taking a diuretic

Ask a doctor or pharmacist before use if you are
- under a doctor's care for any serious condition
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product
take with food or milk if stomach upset occurs

Stop use and ask a doctor if
- you experience any of the following signs of stomach bleeding:
  - feel faint
  - vomit blood
  - have bloody or black stools
  - have stomach pain that does not get better
- you have symptoms of heart problems or stroke:
  - chest pain
  - trouble breathing
  - weakness in one part or side of body
  - slurred speech
  - leg swelling
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding,
ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children.
In case of overdose, get medical help or contact a Poison Control Center right away.

DIRECTIONS
- do not take more than directed
- the smallest effective dose should be used
- adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 1 capsule, 2 capsules may be used
- do not exceed 6 capsules in 24 hours, unless directed by a doctor
- children under 12 years: ask a doctor
APPENDIX 2. Example Pediatric Ibuprofen Drug Facts Label

USES
temporarily:
  • reduces fever
  • relieves minor aches and pains due to the common cold, flu, sore throat, headaches and toothaches

WARNINGS

Allergy alert
Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
  • hives
  • facial swelling
  • asthma (wheezing)
  • shock
  • skin reddening
  • rash
  • blisters
If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning
This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if your child:
  • has had stomach ulcers or bleeding problems
  • takes a blood thinning (anticoagulant) or steroid drug
  • takes other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
  • takes more or for a longer time than directed

Heart attack and stroke warning
NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

Sore throat warning
Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult doctor promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by doctor.

Do not use
  • if the child has ever had an allergic reaction to ibuprofen or any other pain reliever/fever reducer
  • right before or after heart surgery
Ask a doctor before use if
- stomach bleeding warning applies to your child
- child has a history of stomach problems, such as heartburn
- child has problems or serious side effects from taking pain relievers or fever reducers
- child has not been drinking fluids
- child has lost a lot of fluid due to vomiting or diarrhea
- child has high blood pressure, heart disease, liver cirrhosis, kidney disease, or had a stroke
- child has asthma
- child is taking a diuretic

Ask a doctor or pharmacist before use if the child is
under a doctor's care for any serious condition taking any other drug

When using this product
take with food or milk if stomach upset occurs

Stop use and ask a doctor if
- child experiences any of the following signs of stomach bleeding:
  o feels faint
  o vomits blood
  o has bloody or black stools
  o has stomach pain that does not get better
- child has symptoms of heart problems or stroke:
  o chest pain
  o trouble breathing
  o weakness in one part or side of body
  o slurred speech
  o leg swelling
- the child does not get any relief within first day (24 hours) of treatment
- fever or pain gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. (1-800-222-1222)

DIRECTIONS
- this product does not contain directions or complete warnings for adult use
- do not give more than directed
- shake well before using
- find right dose on chart below. If possible, use weight to dose; otherwise use age.
- mL = milliliter
- measure with the dosing device provided. Do not use with any other device.
• dispense liquid slowly into the child's mouth, toward the inner cheek
• if needed, repeat dose every 6-8 hours
• do not use more than 4 times a day
APPENDIX 3. Example Naproxen Sodium Adult Drug Facts Label

USES
temporarily relieves minor aches and pains due to:
- minor pain of arthritis
- muscular aches
- backache
- menstrual cramps
- headache
- toothache
- the common cold
- temporarily reduces fever

WARNINGS

Allergy alert
Naproxen sodium may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters
If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning
This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:
- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Heart attack and stroke warning
NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

Do not use
- if you have ever had an allergic reaction to any other pain reliever/ fever reducer
- right before or after heart surgery
Ask a doctor before use if
- the stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, or had a stroke
- you are taking a diuretic
- you have problems or serious side effects from taking pain relievers or fever reducers
- you have asthma

Ask a doctor or pharmacist before use if you are
- under a doctor's care for any serious condition
- taking any other drug

When using this product
- take with food or milk if stomach upset occurs

Stop use and ask a doctor if
- you experience any of the following signs of stomach bleeding:
  - feel faint
  - vomit blood
  - have bloody or black stools
  - have stomach pain that does not get better
- you have symptoms of heart problems or stroke:
  - chest pain
  - trouble breathing
  - weakness in one part or side of body
  - slurred speech
  - leg swelling
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- you have difficulty swallowing
- it feels like the pill is stuck in your throat
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use naproxen sodium during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
DIRECTIONS

- do not take more than directed
- the smallest effective dose should be used
- drink a full glass of water with each dose
APPENDIX 4. Example Aspirin (Enteric Coated) 81 mg Drug Facts Label

USES
- for the temporary relief of minor aches and pains or as recommended by your doctor. Because of its delayed action, this product will not provide fast relief of headaches or other symptoms needing immediate relief.
- ask your doctor about other uses for 81 mg aspirin

WARNINGS

Reye's syndrome
Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness.

Allergy alert
Aspirin may cause a severe allergic reaction which may include:
- hives
- facial swelling
- asthma (wheezing)
- shock

Stomach bleeding warning
This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you
- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use if you are allergic to aspirin or any other pain reliever/ fever reducer

Ask a doctor before use if
- stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
- you are taking a diuretic
- you have asthma

Ask a doctor or pharmacist before use if you are taking a prescription drug for
- gout
- diabetes
- arthritis

**Stop use and ask a doctor if**
- an allergic reaction occurs. Seek medical right away.
- you experience any of the following signs of stomach bleeding:
  - feel faint
  - vomit blood
  - have bloody or black stools
  - have stomach pain that does not get better
- pain gets worse or lasts more than 10 days
- redness or swelling is present
- new symptoms occur
- ringing in the ears or a loss of hearing occurs

**If pregnant or breast-feeding,** ask a health professional before use. It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

**DIRECTIONS**
- drink a full glass of water with each dose
- adults and children 12 years and over: take 4 to 8 tablets every 4 hours not to exceed 48 tablets in 24 hours unless directed by a doctor
- children under 12 years: consult a doctor
APPENDIX 5. Example Aspirin 500 mg Drug Facts Label

USES
temporarily relieves
  • headache
  • pain and fever of colds
  • muscle pain
  • menstrual pain
  • toothache
  • minor pain of arthritis

WARNINGS

Reye’s syndrome: Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye’s syndrome, a rare but serious illness.

Allergy alert: Aspirin may cause a severe allergic reaction which may include:
  • hives
  • facial swelling
  • asthma (wheezing)
  • shock

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you
  • are age 60 or older
  • have had stomach ulcers or bleeding problems
  • take a blood thinning (anticoagulant) or steroid drug
  • take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
  • have 3 or more alcoholic drinks every day while using this product
  • take more or for a longer time than directed

Do not use
  • if you are allergic to aspirin or any other pain reliever/fever reducer
  • if you have ever had an allergic reaction to this product or any of its ingredients

Ask a doctor before use if
  • stomach bleeding warning applies to you
  • you have a history of stomach problems, such as heartburn
  • you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
  • you are taking a diuretic
  • you have asthma
Ask a doctor or pharmacist before use if you are taking a prescription drug for

- gout
- diabetes
- arthritis

Stop use and ask a doctor if

- an allergic reaction occurs. Seek medical help right away.
- you experience any of the following signs of stomach bleeding:
  - feel faint
  - vomit blood
  - have bloody or black stools
  - have stomach pain that does not get better
- pain gets worse or lasts more than 10 days
- redness or swelling is present
- fever lasts more than 3 days
- new symptoms occur
- ringing in the ears or a loss of hearing occurs

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

DIRECTIONS

- drink a full glass of water with each dose
- adults and children 12 years and over: take 1 or 2 tablets every 4 to 6 hours not to exceed 8 tablets in 24 hours
- children under 12 years: consult a doctor
PRECAUTIONS

General

Renal Failure: Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 ml/min).

Hepatic Failure: Avoid aspirin in patients with severe hepatic insufficiency.

Salicylism: Avoid aspirin in patients with salicylate intoxication.

Laboratory Tests

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Drug Interactions

Acetylsalicylic Acid (ASA) Inhibitors: The hypertensive and hypotensive effects of ASA inhibitors may be diminished by the concurrent administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetaminophen: Concomitant use of aspirin and acetaminophen can lead to higher serum concentrations of acetaminophen (and toxicity) due to competition at the liver for metabolism.

Acetazolamide: The effectiveness of diuretics in patients with chronic renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of prostaglandin synthetase, leading to decreased renal blood flow and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of prostaglandin synthetase, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Salicylate can inhibit clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impairment.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): The concomitant use of aspirin with other NSAIDs should be avoided because this may increase bleeding or lead to decreased renal function.

Oxytetracycline: Moderate doses of aspirin may increase the effectiveness of oral oxytetracycline.

Unlabeled Use of Unlabeled Salicylates: Salicylates antagonize the anticoagulant effect of warfarin and other anticoagulants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of aspirin for 68 weeks at 0.5 percent in the feed of rats was not carcinogenic. In the Ames Salmonella assay, aspirin was not mutagenic, however, aspirin did induce chromosome aberrations in cultured human fibroblasts. Aspirin inhibits ovulation in rats. (See Pregnancy.)

Pregnancy

Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hematologic mechanisms, decreased birth weight, and with perinatal mortality.

Labor and Delivery

Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Nursing Mothers

Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, placental abortion, and bleeding in nursing infants.

Pediatric Use

Pediatric dosing recommendations for juvenile rheumatoid arthritis are based on well-controlled clinical studies. An initial dose of 90-100 mg/kg/day in divided doses, with an increase as needed for anti-inflammatory efficacy (target plasma salicylate levels of 150-300 mcg/ml). At high doses (i.e., plasma levels of greater than 200 mcg/ml), the incidence of toxicity increases.

ADVERSE REACTIONS

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature. (See Warnings.)

Cardiovascular: Dysrhythmias, hypotension, myocardial infarction.


Drug Abuse and Dependence

Aspirin is not a narcotic. There is no known potential for addiction associated with the use of aspirin.

OVERDOSE

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylate overdose (salicylism) include tinnitus (ringing in the ears), occipital plasma concentrations approaching 100 mg/ml. Plasma concentrations of aspirin above 300 mcg/ml are clearly toxic. Severe toxic effects are associated with levels above 400 mcg/ml. (See Clinical Pharmacology.) A single lethal dose of aspirin in adults has been reported to be 40-60 mg/kg, with fatalities having occurred at blood levels of 10-20 mg/ml. For real or suspected overdose, a Pulmonary Intensive Care Center should be contacted immediately. Careful medical management is essential.

Signs and Symptoms: In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hypertension and dehydration. Respiratory alkalosis occurs early while hyperperfusion is present, but is quickly followed by metabolic acidosis.

Treatment: Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid-base disturbance. Gastric emptying and/or lavage is recommended as soon as possible after ingestion, even if the patient has vomiting spontaneously. After lavage and/or emesis, administration of activated charcoal, as a slurry, is beneficial. If less than 3 hours have passed since ingestion, charcoal absorption should not be employed prior to gastric lavage.

Severely of salicylate intoxication is determined by measuring the blood salicylate level. Acid-base status should be closely followed with serial blood gases and serum pH measurements. Fluid and electrolyte balance should also be maintained.

In severe cases, hypothermia and hypovolemia are the major immediate threats to life. Children should be spotsed with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkali diuresis of salicylate if renal function is normal. Intusion of glucose may be required to control hypoglycemia.

Hemodialysis and peritoneal dialysis can be performed to reduce the body drug content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be instituted in infants and young children.

DOSE AND ADMINISTRATION

Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted.

Anti-inflammator and analgesic dosages should be individualized. When aspirin is used in high doses, the development of tinnitus may be used as a clinical sign of elevated plasma salicylate levels except in patients with high frequency hearing loss.

Indications for Use and Dose: 30-35 mcg once a day. Continue therapy indefinitely.

Suspected Acute MI:

The initial dose of 160-162.5 mg is administered as soon as an MI is suspected. The maintenance dose of 160-162.5 mg a day is confirmed for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.

Prevention of Recurrent MI:

75-105 mcg once a day. Continue therapy indefinitely.

Unstable Angina Pectoris:

75-105 mcg once a day. Continue therapy indefinitely.

Chronic Stable Angina Pectoris:

75-105 mcg once a day. Continue therapy indefinitely.

CABG:

325 mg daily starting 6 hours post-procedure. Continue therapy for one year post-procedure.

PTCA:

The initial dose of 325 mg should be given 2 hours pre-surgery. Maintenance dose is 160-325 mg daily. Continue therapy indefinitely.

Cranial Endarterectomy:

Doses of 300 mg once daily to 600 mg twice daily, started pre-surgery, are recommended. Continue therapy indefinitely.

Rheumatoid Arthritis:

The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/ml. At high doses (i.e., plasma levels of greater than 200 mcg/ml), the incidence of toxicity increases.

Juvenile Rheumatoid Arthritis:

Initial dose is 0.5-1.0 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 120-150 mcg/ml. At high doses (i.e., plasma levels of greater than 200 mcg/ml), the incidence of toxicity increases.

Spinal Dural Puncture:

Up to 4 g per day in divided doses.

Cataracts:

Up to 3 g per day in divided doses.

Arthritis and Pain of SLE:

The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/ml. At high doses (i.e., plasma levels of greater than 200 mcg/ml), the incidence of toxicity increases.

HOW SUPPLIED

BAYER SAFETY COATED REGULAR STRENGTH ASPIRIN, 325 MG

Available in bottles of 360. Tablet identification: capsule shaped tablets, yellow, “Bayer 325” printed on one side. BAYER LOW DOSE SAFETY COATED ASPIRIN, 81 MG

Available in bottles of 22, 120, 200, and 360.

Tablet identification: round tablet, yellow, “81” printed on one side. BAYER CHENABE LOW DOSE ASPIRIN – CHERRY FLAVORED, 81 MG

Available in bottles of 36. Tablet identification: round tablet, pink, with Bayer Cross Logo appearing on both sides. BAYER CHENABE LOW DOSE ASPIRIN – ORANGE FLAVORED, 81 MG

Available in bottles of 36 and a value pack of 5 packages of 10 (360). Tablet identification: round tablet, orange, with Bayer Cross Logo appearing on both sides.

BAYER WOMEN’S LOW DOSE ASPIRIN WITH A CALCIUM CARBONATE BUFFER, 81 MG


GENUINE BAYER ASPIRIN, 325 MG

Available in bottles of 24, 50, 100, 200, and 360.

Tablet identification: round tablet, white, with Bayer Cross Logo appearing on both sides.

Storage Conditions: Store at room temperature. Avoid excessive heat above 40°C (104°F).

Bayer Healthcare LLC, Whippany, NJ 07101

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Revised: Dec. 15, 2018 G6292