

ATTACHMENT 1

Attachment 1
Proposed Professional Aspirin Label

Table 1. Requested Changes to Professional Aspirin Labeling

Aspirin Professional Labeling (21 CFR § 343.80)	Brief Explanation of Proposed Labeling Changes and Supporting References
<p>COMPREHENSIVE PRESCRIBING INFORMATION</p> <p>DESCRIPTION</p> <p><i>(Insert the proprietary name and the established name (if any) of the drug, type of dosage form (followed by the phrase "for oral administration"), the established name(s) and quantity of the active ingredient(s) per dosage unit, the total sodium content in milligrams per dosage unit if the sodium content of a single recommended dose is 5 milligrams or more, the established name(s) (in alphabetical order) of any inactive ingredient(s) which may cause an allergic hypersensitivity reaction, the pharmacological or therapeutic class of the drug, and the chemical name(s) and structural formula(s) of the drug.)</i> Aspirin is an odorless white, needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary-odor. It is highly lipid soluble and slightly soluble in water.</p>	<p>No change requested</p>
<p>CLINICAL PHARMACOLOGY</p> <p><i>Mechanism of Action: Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclo-oxygenase via acetylation. Enteric coated aspirin products are erratically absorbed from the GI tract. Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A₂. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I₂ (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.</i></p>	<p>The proposed change to the Clinical Pharmacology/Mechanism of Action section is consistent with: Aspirin information, PRAVIGARD PAC, Issued May 2003. The PRAVIGRAD PAC label reflects the Agency's most recent aspirin labeling.</p>
<p>PHARMACOKINETICS</p> <p><i>Absorption:</i> In general, immediate-release aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-2 hours of dosing (see PHARMACOKINETICS--<i>Metabolism</i>). The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents), and other physiologic factors. Enteric coated aspirin products are erratically absorbed from the GI tract.</p> <p><i>Distribution:</i> Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues. The</p>	<p>No change requested</p>

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<p>PHARMACOKINETICS, cont</p> <p>highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is concentration-dependent, i.e., non-linear. At low concentrations (< 100 micrograms/milliliter ($\mu\text{g/mL}$)), approximately 90 percent % of plasma salicylate is bound to albumin while at higher concentrations (> 400 g/mL), only about 75 percent % is bound. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approximating 200 g/mL. Severe toxic effects are associated with levels > 400 b/mL. (See ADVERSE REACTIONS and OVERDOSAGE.)</p> <p><i>Metabolism:</i> Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 grams (g)), the plasma half-life may be increased to over 20 hours.</p> <p><i>Elimination:</i> The elimination of salicylic acid follows zero order pharmacokinetics; (i.e., the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5 percent to > 80 percent. Alkalinization of the urine is a key concept in the management of salicylate overdose. (SEE OVERDOSAGE.) Following therapeutic doses, approximately 10 % percent is found excreted in the urine as salicylic acid, 75 % percent as salicyluric acid, and 10 % percent as the phenolic and 5 % percent acyl glucuronides of salicylic acid.</p> <p><i>Pharmacodynamics:</i> Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A₂. Non-acetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I₂ (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.</p> <p>At higher doses aspirin is an effective anti-inflammatory agent, partially due to inhibition of inflammatory mediators via cyclo-oxygenase inhibition in peripheral tissues. In vitro studies suggest that other mediators of inflammation may also be suppressed by aspirin administration, although the precise mechanism of action has not been elucidated. It is this non-specific suppression of cyclo-oxygenase activity in peripheral tissues following large doses that leads to its primary side effect of gastric irritation. (See ADVERSE REACTIONS.)</p>	<p>The proposed change to the Pharmacokinetics/Distribution section is consistent with: Aspirin information, PRAVIGARD PAC, Issued May 2003. The PRAVIGRAD PAC label reflects the Agency's most recent aspirin labeling.</p> <p>No change requested</p> <p>The proposed change to the Pharmacokinetics/Elimination section is consistent with: Aspirin information, PRAVIGARD PAC, Issued May 2003. The PRAVIGRAD PAC label reflects the Agency's most recent aspirin labeling.</p>

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<p>CLINICAL STUDIES</p> <p><u>Doses of aspirin in the range of 50 –150 mg daily are as effective as higher doses for the prevention of serious vascular events (nonfatal stroke, nonfatal myocardial infarction or vascular death).</u></p> <p><u>In the Antithrombotic Trialists' Collaboration (ATC) meta-analysis of 287 studies involving 212,000 patients, as aspirin doses increased above 75 mg, there was no improvement in efficacy for serious vascular events. Among the trials of higher daily doses of aspirin vs. no aspirin, no particular range of aspirin dose was preferable for the prevention of serious vascular events. The proportional reduction in vascular events was 19% with 500 – 1500 mg daily, 25% with 160–325 mg daily, and 32% with 75–199 daily.</u></p> <p><i>Ischemic Stroke and Transient Ischemic Attack (TIA):</i> In clinical trials of subjects with TIA's due to fibrin platelet emboli or ischemic stroke, aspirin has been shown to significantly reduce the risk of the combined endpoint of stroke or death and the combined endpoint of TIA, stroke, or death by about 13-18 percent %.</p> <p><i>Suspected Acute Myocardial Infarction (MI):</i> In a large, multi-center study of aspirin, streptokinase, and the combination of aspirin and streptokinase in 17,187 patients with suspected acute MI, aspirin treatment produced a 23 percent % reduction in the risk of vascular mortality. Aspirin was also shown to have an additional benefit in patients given a thrombolytic agent.</p> <p><i>Prevention of Recurrent MI and Unstable Angina Pectoris:</i> These indications are supported by the results of six large, randomized, multi-center, placebo-controlled trials of predominantly male post-MI subjects and one randomized placebo-controlled study of men with unstable angina pectoris. Aspirin therapy in MI subjects was associated with a significant reduction (about 20 percent %) in the risk of the combined endpoint of subsequent death and/or nonfatal reinfarction in these patients. In aspirin-treated unstable angina patients the event rate was reduced to 5 percent from the 10 percent % rate in the placebo group.</p> <p><i>Chronic Stable Angina Pectoris:</i> In a randomized, multi-center, double-blind trial designed to assess the role of aspirin for prevention of MI in patients with chronic stable angina pectoris, aspirin significantly reduced the primary combined endpoint of nonfatal MI, fatal MI, and sudden death by 34 percent %. The secondary endpoint for vascular events (first occurrence of MI, stroke, or vascular death) was also significantly reduced (32 percent %).</p>	<p>The proposed change to the Warnings/GI Side Effects section is consistent with the following scientific/clinical data: Attachment 3: Integrated Summary of Efficacy Antithrombotic Trialists' Collaboration (ATC), 2002</p> <p>The proposed change to the Clinical Studies/Transient Ischemic Attack section is consistent with: Aspirin information, PRAVIGARD PAC, Issued May 2003. The PRAVIGRAD PAC label reflects the Agency's most recent aspirin labeling.</p> <p>The proposed change to the Clinical Studies/Myocardial Infarction section is consistent with: Aspirin information, PRAVIGARD PAC, Issued May 2003. The PRAVIGRAD PAC label reflects the Agency's most recent aspirin labeling.</p> <p>The proposed change to the Clinical Studies/Recurrent MI and Unstable Angina Pectoris section is consistent with: Aspirin information, PRAVIGARD PAC, Issued May 2003. The PRAVIGRAD PAC label reflects the Agency's most recent aspirin labeling.</p> <p>The proposed change to the Clinical Studies/Recurrent MI and Chronic Angina Pectoris section is consistent with: Aspirin information, PRAVIGARD PAC, Issued May 2003. The PRAVIGRAD PAC label reflects the Agency's most recent aspirin labeling.</p>

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Aspirin Professional Labeling (21 CFR § 343.80)	Brief Explanation of Proposed Labeling Changes and Supporting References
<p>CLINICAL STUDIES, cont.</p> <p><i>Revascularization Procedures:</i> Most patients who undergo coronary artery revascularization procedures have already had symptomatic coronary artery disease for which aspirin is indicated. Similarly, patients with lesions of the carotid bifurcation sufficient to require carotid endarterectomy are likely to have had a precedent event. Aspirin is recommended for patients who undergo revascularization procedures if there is a preexisting condition for which aspirin is already indicated.</p> <p><i>Rheumatologic Diseases:</i> In clinical studies in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis and osteoarthritis, aspirin has been shown to be effective in controlling various indices of clinical disease activity.</p>	<p>No change requested</p> <p>No change requested</p>
<p>ANIMAL TOXICOLOGY</p> <p>The acute oral 50 percent lethal dose in rats is about 1.5 g/kilogram (kg) and in mice 1.1 g/kg. Renal papillary necrosis and decreased urinary concentrating ability occur in rodents chronically administered high doses. Dose-dependent gastric mucosal injury occurs in rats and humans. Mammals may develop aspirin toxicosis associated with GI symptoms, circulatory effects, and central nervous system depression. (See OVERDOSAGE.)</p>	<p>No change requested</p>
<p>INDICATIONS AND USAGE</p> <p><i>Vascular Indications (Ischemic Stroke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris, and Chronic Stable Angina Pectoris):</i> Aspirin is indicated to: (1) 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, (2) reduce the risk of vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.</p> <p><i>Revascularization Procedures (Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), and Carotid Endarterectomy):</i> Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.</p> <p><i>Rheumatologic Disease Indications (Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Spondyloarthropathies, Osteoarthritis, and the Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE)):</i> Aspirin is indicated for the relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with SLE.</p>	<p>No change requested</p>

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<p>CONTRAINDICATIONS</p> <p><i>Allergy:</i> Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).</p> <p><i>Reye's Syndrome:</i> Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.</p>	<p>No change requested</p>
<p>WARNINGS</p> <p><i>Alcohol Warning:</i> Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.</p> <p><i>Coagulation Abnormalities:</i> Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.</p> <p><i>GI Side Effects:</i> GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur. <u>Aspirin doses of 75-150 mg daily have been shown to have a lower risk of major bleeding events, when compared with aspirin doses of >151 mg.</u></p> <p><i>Peptic Ulcer Disease:</i> Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.</p> <p><u>Pregnancy: Pregnant women should only take aspirin if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on 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 hemostasis mechanisms, decreased birth weight and with perinatal mortality.</u></p>	<p>No change requested</p> <p>No change requested</p> <p>The proposed change to the Warnings/GI Side Effects section is consistent with the following scientific/clinical data: Attachment 2: Integrated Summary of Safety Peters et al., 2003; Topol et al., 2003; Serebruany et al., 2004 Serebruany et al., 2005</p> <p>No change requested</p> <p>The proposed addition of the Warnings/Pregnancy section is consistent with: Aspirin information, PRAVIGARD PAC, Issued May 2003. The PRAVIGRAD PAC label reflects the Agency's most recent aspirin labeling.</p>

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<p>PRECAUTIONS</p> <p>General</p> <p><i>Renal Failure:</i> Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).</p> <p><i>Hepatic Insufficiency:</i> Avoid aspirin in patients with severe hepatic insufficiency.</p> <p><i>Sodium Restricted Diets:</i> Patients with sodium-retaining states, such as congestive heart failure or renal failure, should avoid sodium-containing buffered aspirin preparations because of their high sodium content.</p> <p><i>Laboratory Tests:</i> Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.</p> <p><u>Information for Patients:</u> Patients should be advised to report to their physician any conditions that may increase the risk of bleeding (see WARNINGS: Coagulation Abnormalities and GI Side Effects).</p> <p>Drug Interactions</p> <p><i>Angiotensin Converting Enzyme (ACE) Inhibitors:</i> The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.</p> <p><i>Acetazolamide:</i> Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.</p> <p><i>Anticoagulant Therapy (Heparin and Warfarin):</i> Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.</p> <p><i>Anticonvulsants:</i> Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.</p> <p><i>Beta Blockers:</i> The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.</p> <p><i>Diuretics:</i> 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 renal prostaglandins, leading to decreased renal blood</p>	<p>No change requested</p> <p>The proposed addition of the Precautions/General section is consistent with: Aspirin information, PRAVIGARD PAC, Issued May 2003. The PRAVIGRAD PAC label reflects the Agency's most recent aspirin labeling.</p> <p>No change requested</p>

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<p>PRECAUTIONS, cont. flow and salt and fluid retention. <i>Methotrexate:</i> Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired. Nonsteroidal Anti-inflammatory Drugs (NSAID's): The concurrent use of aspirin with other NSAID's should be avoided because this may increase bleeding or lead to decreased renal function. <i>Oral Hypoglycemics:</i> Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia. <i>Uricosuric Agents (Probenecid and Sulfipyrazone):</i> Salicylates antagonize the uricosuric action of uricosuric agents.</p> <p><i>Carcinogenesis, Mutagenesis, Impairment of Fertility:</i> 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 <i>Pregnancy.</i>)</p> <p><i>Pregnancy:</i> Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAID's 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 hemostasis mechanisms, decreased birth weight, and with perinatal mortality.</p> <p><i>Labor and Delivery:</i> 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.</p> <p><i>Nursing Mothers:</i> Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.</p> <p><i>Pediatric Use:</i> Pediatric dosing recommendations for juvenile rheumatoid arthritis are based on well-controlled clinical studies. An initial dose of 90-130 mg/kg/day in divided doses, with an increase as needed for anti-inflammatory efficacy (target plasma salicylate levels of 150-300 µg/mL) are effective. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.</p>	<p>No change requested</p> <p>The proposed change of the Precautions/General/Pregnancy section is consistent with Aspirin information, PRAVIGARD PAC, Issued May 2003. <i>Pregnancy</i> moved to end of WARNINGS.</p> <p>No change requested</p> <p>No change requested</p> <p>No change requested</p>

Table 1. Requested Changes to Professional Aspirin Labeling

Aspirin Professional Labeling (21 CFR § 343.80)	Brief Explanation of Proposed Labeling Changes and Supporting References
<p>ADVERSE REACTIONS</p> <p>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.)</p> <p><i>Body as a Whole:</i> Fever, hypothermia, thirst.</p> <p><i>Cardiovascular:</i> Dysrhythmias, hypotension, tachycardia.</p> <p><i>Central Nervous System:</i> Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.</p> <p><i>Fluid and Electrolyte:</i> Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis.</p> <p><i>Gastrointestinal:</i> Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's Syndrome, pancreatitis.</p> <p><i>Hematologic:</i> Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.</p> <p><i>Hypersensitivity:</i> Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.</p> <p><i>Musculoskeletal:</i> Rhabdomyolysis.</p> <p><i>Metabolism:</i> Hypoglycemia (in children), hyperglycemia.</p> <p><i>Reproductive:</i> Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.</p> <p><i>Respiratory:</i> Hyperpnea, pulmonary edema, tachypnea.</p> <p><i>Special Senses:</i> Hearing loss, tinnitus. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.</p> <p><i>Urogenital:</i> Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.</p> <p><u>Prospective observations in the context of two clinical trials and two large-scale meta-analyses consistently showed aspirin doses of 75 –150 mg daily to have a lower risk of major bleeding events, particularly GI bleeding, when compared with aspirin doses of >151 mg.</u></p> <p><u>These trials were the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial of 12,562 patients with acute coronary syndrome (ACS) without ST-segment elevation and the Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial of 9190 patients with coronary and cerebrovascular disease.</u></p> <p><u>The rate of major bleeding events from the CURE trial for placebo plus aspirin was dose-dependent on aspirin: ≤100=1.86%; 101-199 mg=2.82%; ≥200 mg=3.67%. The major bleeding event rate for clopidogrel plus aspirin was also dose-dependent</u></p>	<p>No change requested</p> <p>The proposed change to the Adverse Reactions section is consistent with the following scientific/clinical data: Attachment 2: Integrated Summary of Safety Peters et al., 2003; Topol et al., 2003; Serebruany et al., 2004 Serebruany et al., 2005</p>

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ADVERSE REACTIONS, cont.
on aspirin: ≤ 100 mg=2.97%; 101-199 mg=3.5%; ≥ 200 mg=4.86% (see Table 1).

Table 1. Percent Incidence of Major and Life-Threatening Bleeding by Various Doses of Aspirin

Major Bleeding Complications	Percent Incidence
Aspirin ≤ 100 mg/day	1.86
Aspirin 101-199 mg/day	2.82
Aspirin ≥ 200 mg/day	3.67
p-value for trend	<0.0001
Adjusted OR for 101-199 mg/day vs. ≤ 100 mg/day	1.52 (1.00 to 2.31)
Adjusted OR for ≥ 200 mg/day vs. ≤ 100 mg/day	1.70 (1.22 to 2.59)
Life-Threatening Bleeding Complications	
Aspirin ≤ 100 mg/day	1.26
Aspirin 101-199 mg/day	1.90
Aspirin ≥ 200 mg/day	2.37
p-value for trend	0.004
Adjusted OR for 101-199 mg/day vs. ≤ 100 mg/day	1.48 (0.89 to 2.46)
Adjusted OR for ≥ 200 mg/day vs. ≤ 100 mg/day	1.64 (1.04 to 2.59)

Abbreviations: OR=odds ratio

Within the placebo plus aspirin group of the BRAVO trial, the incidence of serious bleeding was 2.4% among patients taking 75-162 mg of aspirin daily and 3.3% among patients taking > 162 mg of aspirin daily. The incidence of any bleeding was 11.1% among patients taking 75-162 mg of aspirin daily and 15.4% among patients taking > 162 mg of aspirin daily. Transfusion was required for 1.0% of the patients taking 75-162 mg of aspirin daily and 9.0% among patients taking > 162 mg of aspirin daily. Transfusion was required for 3.4% of the patients taking 75-162 mg of aspirin daily and 5.9% of patients taking > 162 mg of aspirin (see Table 2).

Table 2. Outcomes by Aspirin Dose in Placebo Study Drug Patients

	Low Dose, 75-162 mg/d (n=2410)	Higher Dose > 162 mg/d (n=2179)
Serious bleeding	2.4	3.3
Any bleeding	11.1	15.4
Transfusion	1.0	2.0

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<p>DRUG ABUSE AND DEPENDENCE</p> <p>Aspirin is non-narcotic. There is no known potential for addiction associated with the use of aspirin.</p>	<p>The proposed change of the DRUG ABUSE AND DEPENDENCE section is consistent with Aspirin information, PRAVIGARD PAC, issued May 2003. The PRAVIGARD PAC label reflects the Agency's most recent aspirin labeling.</p>
<p>OVERDOSAGE</p> <p>Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approaching 200 µg/mL. Plasma concentrations of aspirin above 300 µg/mL are clearly toxic. Severe toxic effects are associated with levels above 400 µg/mL. (See CLINICAL PHARMACOLOGY.) A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately. Careful medical management is essential.</p> <p><i>Signs and Symptoms:</i> In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis.</p> <p><i>Treatment:</i> 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 vomited 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 adsorption should not be employed prior to emesis and lavage.</p> <p>Severity of aspirin intoxication is determined by measuring the blood salicylate level. Acid-base status should be closely followed with serial blood gas and serum pH measurements. Fluid and electrolyte balance should also be maintained.</p> <p>In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia.</p> <p>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 indicated in infants and young children.</p>	<p>No change requested</p>
<p>DOSAGE AND ADMINISTRATION</p> <p>Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted. Anti-inflammatory 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.</p>	<p>No change requested</p>

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<p>DOSAGE AND ADMINISTRATION, cont.</p> <p>—Ischemic Stroke and TIA: 81 (this is our product — base on Pravigard finding for 81 mg) mg once a day. Continue therapy indefinitely.</p> <p>Prevention of Recurrent MI: 75-325 mg once a day. Continue therapy indefinitely.</p> <p>Unstable Angina Pectoris: 75-325 mg once a day. Continue therapy indefinitely.</p> <p>Chronic Stable Angina Pectoris: 75-325 mg once a day. Continue therapy indefinitely.</p> <p><u>Chronic Dosing: Aspirin doses of 50–150 mg daily carry a lower risk of major bleeding events, particularly GI bleeding, when compared with doses >151 mg daily, while providing comparable efficacy (See WARNINGS: GI Side Effects). The recommended aspirin dose for chronic administration is 75–150 mg daily, which is safe and effective for Prevention of Recurrent MI and for Treatment of Unstable Angina Pectoris or Chronic Stable Angina Pectoris, and a dose of 50–150 mg daily, which is safe and effective for Ischemic Stroke and TIA. Aspirin is recommended for patients who undergo Revascularization Procedures, such as Coronary Artery Bypass Grafting, Angioplasty, or Carotid Endarterectomy. If there is a pre-existing condition for which aspirin is already indicated, therapy should be continued indefinitely.</u></p>	<p>The proposed change to the Dosage and Administration section is consistent with the following scientific/clinical data: Attachment 2: Integrated Summary of Safety Attachment 3: Integrated Summary of Efficacy Peters et al., 2003; Topol et al., 2003; Serebruany et al., 2004 Serebruany et al., 2005</p>
<p><i>Acute Dosing: Suspected Acute MI:</i> 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 continued for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.</p>	<p>No change requested</p>
<p>Revascularization Procedures:</p> <p>CABG: 325 mg daily starting 6 hours post-procedure. Continue therapy for 1 year post-procedure.</p> <p>PTCA: The initial dose of 325 mg should be given 2 hours pre-surgery. Maintenance dose is 160-325 mg daily. Continue therapy indefinitely.</p> <p>Carotid Endarterectomy: Doses of 80 mg once daily to 650 mg twice daily, started presurgery, are recommended. Continue therapy indefinitely.</p>	<p>No change requested</p>
<p>Rheumatologic Diseases</p> <p>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 g/mL. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.</p> <p>Juvenile Rheumatoid Arthritis: Initial dose is 90-130 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 g/mL. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.</p>	<p>No change requested</p>

Table 1. Requested Changes to Professional Aspirin Labeling

Aspirin Professional Labeling (21 CFR § 343.80)	Brief Explanation of Proposed Labeling Changes and Supporting References
<p>DOSAGE AND ADMINISTRATION, cont.</p> <p><i>Spondyloarthropathies:</i> Up to 4 g per day in divided doses.</p> <p><i>Osteoarthritis:</i> Up to 3 g per day in divided doses.</p> <p><i>Arthritis and Pleurisy of SLE:</i> The initial dose is 3 g a day in divided doses.</p> <p>Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 g/mL. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.</p>	
<p>HOW SUPPLIED</p> <p>– (Insert specific information regarding, strength of dosage form, units in which the dosage form is generally available, and information to facilitate identification of the dosage form as required under Sec. 201.57(k)(1), (k)(2), and (k)(3).) Store in a tight container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).</p>	No change requested