

Meeting Topic: NDAC Meeting on Risks of NSAIDs

**Background Package Submitted by
Wyeth Consumer Healthcare**

Executive Summary

A joint meeting between the FDA and the Nonprescription Drug Advisory Committee (NDAC) is scheduled for September 20, 2002. The purpose of the meeting is to discuss the gastrointestinal (GI) and renal toxicity risks associated with the use of over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) and to determine whether modification to the current label for these products is necessary to address these risks.

Wyeth Consumer Healthcare (WCH), the leading manufacturer of OTC ibuprofen, has prepared an overview of the vast data supporting the safety and efficacy of OTC ibuprofen. These data show that OTC ibuprofen has a long history of safe and effective use by consumers, indicating that the current labeling for OTC ibuprofen has been generally effective in communicating its appropriate use.

Based on data derived from controlled clinical trials, epidemiology studies, and safety surveillance data:

- Not all NSAIDs have the same safety profile;
- For any NSAID, the risk for developing serious events is related to dose and duration of use;
- Ibuprofen has the most favorable GI safety profile of all NSAIDs;
- The approved OTC daily dose of ibuprofen (1200 mg/day) is 37.5% of the maximum daily prescription dose (3200 mg); the OTC dosing regimen of 200 mg to 400 mg has been shown to provide very effective analgesia and is designed to allow for flexibility in dosing where necessary;
- When OTC doses of ibuprofen (200-400 mg/dose; 1200 mg/day) are taken for acute episodes of pain (i.e., up to 10 days), its GI safety profile is even more favorable than at prescription doses, with an extremely low risk of causing serious gastrointestinal events;
 - A meta-analysis of epidemiology studies has shown that when administered at daily doses of 1500 mg-1800 mg, ibuprofen has a relative risk of GI adverse events that is not significantly different from that of the general population (RR=1.42, 95% CI 0.93, 2.15);

- A case-cohort study specifically designed to estimate the relative risk of GI bleeding associated with OTC doses of naproxen sodium and ibuprofen evaluated events which occurred within the first 2 weeks of dosing among those Medicaid patients whose average daily dose was ≤ 600 mg/day of naproxen sodium or ≤ 1200 mg/day of ibuprofen. The analysis showed that the incidence of GI bleeding associated with both drugs was extremely low (0.012% for ibuprofen and 0.026% for naproxen sodium);
- Over the 18 years that ibuprofen has been available OTC, the Agency has received an average of approximately 18 reports per year of GI perforations, ulcers or hemorrhage associated with OTC ibuprofen;
- The frequency of renal side effects with OTC ibuprofen has also been shown to be low (less than 2 cases of renal failure per year), confirming that nonprescription ibuprofen is well tolerated;
- Even though for the past eighteen years non-prescription (OTC) ibuprofen has been subject to the same post-marketing surveillance activities required for prescription drug products, no new, significant health risks to the OTC population have been identified;
- According to data collected and reported by the American Association of Poison Control Centers (AAPCC) from 1987 through 2000, ibuprofen poses significantly less risk than acetaminophen with respect to overdose. Ibuprofen exposures have also resulted in considerably less severe outcomes, and many fewer deaths than acetaminophen.

The excellent safety profile of OTC ibuprofen, generated over 18 years of use by millions of consumers indicates that the current labeling for OTC ibuprofen has been effective in informing consumers of the appropriate conditions for using the product. Consumer use data suggests that the vast majority of consumers follow ibuprofen's label:

- Data from a 2002 Gallup survey indicate that consumers of OTC ibuprofen use an average of only 17.1 pills per month; only 6.5% use > 50 pills/month;
- In a 1996 Attitude and Usage study conducted over a 10-day period, the average number of tablets taken per dose was approximately 2, the average number of tablets taken per day was 3.6 (~ 720 mg); more than 6 tablets per day (>1200 mg) were taken only 8% of the time.

In preparation for the September NDAC meeting, on August 23, 2002, the Agency published its review of the GI and renal safety data for ibuprofen. In their conclusion, the Agency has suggested that modifications to ibuprofen's label are warranted. On August 21, 2002, the Agency published a proposal in the Federal Register recommending that ibuprofen be included in the Tentative Final Monograph for OTC internal analgesic drug products, thereby recognizing it as being generally safe and effective. Importantly, the Agency made its recommendation based on ibuprofen's favorable safety profile, which has been generated with the **current** OTC label. As part of the Agency's proposal, they have also provided explicit wording for more specific GI and renal warnings to the label. As with the label comprehension study conducted in 1983 prior to the approval of OTC ibuprofen, greater specificity in the warnings statements may not necessarily prove to be as effective as the current more general warnings. As such, WCH strongly recommends that any proposed modifications to the label should be adequately tested to ensure the proposed changes actually benefit the consumer. Although WCH has not had sufficient time to consumer test or evaluate all of the proposed modifications, WCH is fully committed to working with the Agency on improving the label for all OTC analgesic products, including ibuprofen, where necessary.

I. Introduction

A joint meeting between the FDA and the Nonprescription Drug Advisory Committee (NDAC) is scheduled for September 20, 2002. The purpose of the meeting is to discuss the gastrointestinal (GI) and renal toxicity risks associated with the use of over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) and to determine whether modification to the current label for these products is necessary to address these risks.

Ibuprofen is a phenylpropionic acid NSAID introduced into the United States in 1974 as a prescription product intended to treat arthritic conditions at daily doses of up to 2400 mg. It was subsequently approved for daily doses of up to 3200 mg/day, and then as a prescription drug to treat mild to moderate pain in 1978.

Since it became available to consumers in 1984, over 100 billion 200 mg tablets of ibuprofen have been sold OTC in the United States alone. Today, consumption of OTC ibuprofen accounts for approximately one third of the market for OTC analgesics. According to a 2002 study by Kauffman et al., ibuprofen continues to be one of the most commonly used drugs in the United States.¹

In preparation for the September NDAC meeting, on August 23, 2002, the Agency published its review of the GI and renal safety data for ibuprofen. In their conclusion, the Agency has suggested that modifications to ibuprofen's label are warranted. On August 21, 2002, the Agency published a proposal in the Federal Register to amend the tentative final monograph (TFM) for OTC internal analgesic, antipyretic and antirheumatic drug products to include ibuprofen as a generally recognized safe and effective analgesic/antipyretic active ingredient for OTC use. The Agency based its recommendation on the very favorable safety profile of OTC ibuprofen. WCH believes that this long history of safe and effective use of OTC ibuprofen indicates that the current OTC labeling has been effective in communicating the appropriate use. As part of their proposal however, the Agency has recommended the addition of more specific GI and renal warnings to the label. For the committee's benefit, WCH has presented the Agency's proposed label changes in this document as part of the overview of the development of the current OTC label. WCH looks forward to discussing

the proposed changes with the Agency and welcomes the opportunity to further explore ways to improve the current label for OTC ibuprofen. As with the label comprehension study conducted in 1983 prior to the approval of OTC ibuprofen, greater specificity in the warnings statements may not necessarily prove to be as effective as the current more general warnings. Accordingly, WCH believes that prior to implementation, any proposed changes must be carefully tested to ensure they achieve the desired communication objective.

Ibuprofen's mode of action, like that of all NSAIDs, is related, in part, to its ability to inhibit cyclooxygenase, and therefore, prostaglandin production. Prostaglandins play an important role in inflammatory processes and pain. They are also involved in maintaining the integrity of the upper gastrointestinal mucosa, and maintaining renal function. NSAIDs clearly provide a therapeutic benefit to the vast majority of individuals. However, in rare instances, usually at prescription doses, they may also produce GI toxicity, including bleeding, ulceration, and perforation, and renal side effects, including renal failure and interstitial nephritis. Accordingly, labeling for all prescription NSAIDs includes detailed warnings describing these risks. While it is clear that such class warnings are appropriate for prescription products, it has become even more clear over the many years of prescription NSAID use that: a) not all NSAIDs have the same safety profile; and b) for any given NSAID, the risk for developing serious events is related to dose and duration of use.

Based primarily on its very favorable GI safety profile at prescription doses, ibuprofen became the first prescription NSAID to be approved by the FDA for OTC use as an analgesic in 1984. At the time of the deliberations that led to its switch, it was anticipated that ibuprofen would demonstrate an improved GI safety profile when used at lower doses over brief periods of time. Accordingly, it was approved for use at single doses of 200-400 mg, up to a maximum of 1200 mg per day. It is important to note that the OTC dose is 37.5% the minimum daily prescription dose. Like the other currently marketed monographed analgesics, the maximum duration for use was limited to 10 days (the duration of use for prescription NSAIDs is not limited).

Since ibuprofen's approval for consumer use, Wyeth Consumer Healthcare (WCH), the leading manufacturer of OTC ibuprofen, has continued to evaluate and assess the efficacy and safety profile of ibuprofen to expand the knowledge base of the effects and consequences of using ibuprofen under OTC conditions. Accordingly, WCH has prepared this document to provide the Agency and the Committee with: a) an overview of the data supporting the safety and efficacy of OTC ibuprofen, b) a history of the development of the current OTC label, and c) consumer use data on OTC ibuprofen.

The data confirm that ibuprofen is the safest prescription NSAID available, although all NSAIDs demonstrate an increased risk of adverse events when used chronically at higher prescription doses. More importantly, as originally expected, when ibuprofen is taken according to the labeled OTC dose and duration of use, the safety profile is even better. There are data to show that even at these low doses, OTC ibuprofen is highly effective in numerous pain states and is more effective than acetaminophen. The labeled dosing instructions, "take 1 (200 mg) tablet every 4 to 6 hours; if pain or fever does not respond to 1 tablet (200 mg), 2 tablets (400 mg) may be used, but do not exceed 6 tablets in 24 hours" allow for flexibility in dosing where necessary, and are supported by data demonstrating a dose-response relationship between 200 mg and 400 mg. As will be shown later in this document, consumer behavior data confirms that the vast majority of consumers follow these instructions.

II. Efficacy of Ibuprofen 200-400 mg

Over its 24-year history of prescription and OTC use, ibuprofen has been studied in numerous clinical analgesic trials encompassing a wide variety of pain conditions including oral surgery pain, general surgery pain, minor arthritic pain, orthopedic pain, muscle aches, sore throat, tension headache, migraine headache and dysmenorrhea. The OTC dosage regimen of 200-400 mg has been evaluated in many of these studies.

Studies in several pain models have shown that ibuprofen 200-400 mg demonstrates a clinically meaningful, as well as statistically significant dose-response relationship (Figures 1-3).²⁻⁵ Both doses provide effective concentrations (EC_{50}) of 6-10 $\mu\text{g/mL}$.^{6,7} within the first

30 minutes and reach peak effects in approximately 1-2 hours. The 400 mg dose provides enhanced analgesia that is reflected in both a greater peak effect and a slightly longer duration of effect compared to the 200 mg dose. The peak analgesic effect appears to be at or near 400 mg (Figure 4).⁷ When evaluating the switch of ibuprofen from prescription to OTC status, an important consideration in assessing the benefit/risk of ibuprofen was evaluating efficacy above the traditional 400 mg dose. A review of the data substantiates that 400 mg of ibuprofen achieves the maximum peak analgesic effect, as higher doses only slightly enhance its duration of action.⁷⁻⁹

Figure 1

Cooper et al., 1977
Oral Surgery
40 patients/treatment

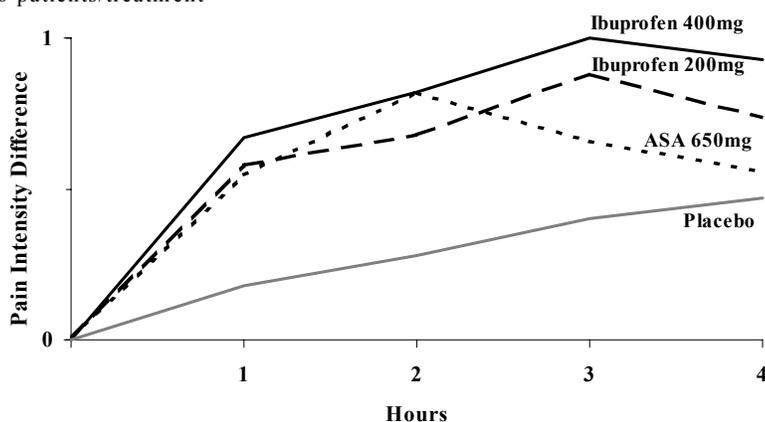


Figure 2

Beaver et al., 1987
Oral Surgery

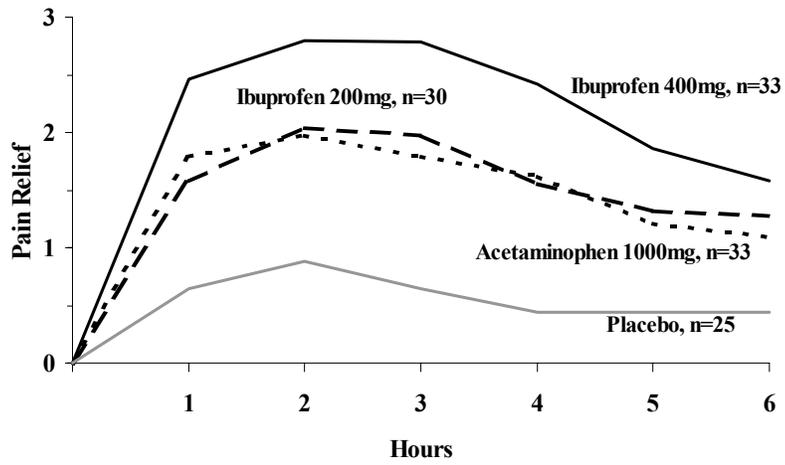


Figure 3

Codispoti et al., 2001
Migraine headache
Severe Baseline Pain Subgroup

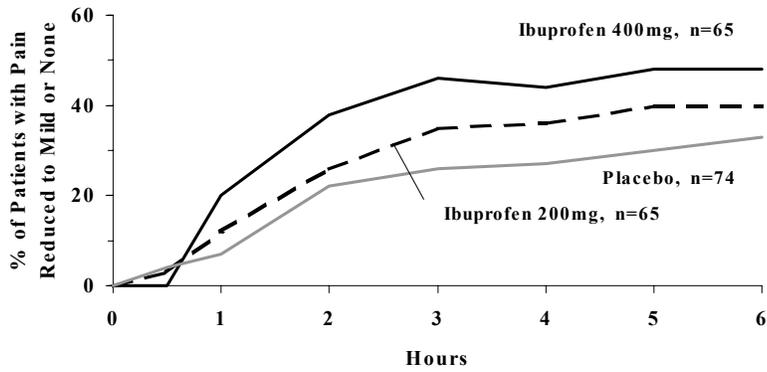
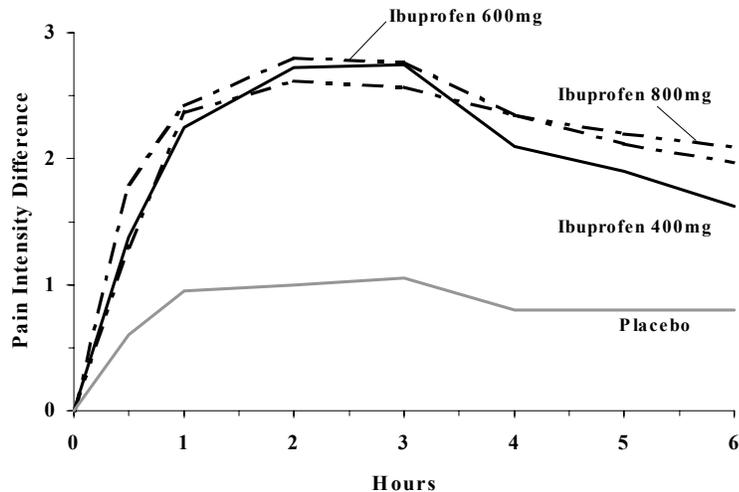


Figure 4

Laska, Sunshine et al., 1986
Oral Surgery
N = 195



Many of the acute pain studies evaluating ibuprofen have been performed with the Dental Impaction Pain Model. This model is widely accepted by expert analgesiologists as the most sensitive, valid and reliable paradigm for assessing relative efficacy and dose-response of NSAID analgesics. Briefly, these studies demonstrate that:

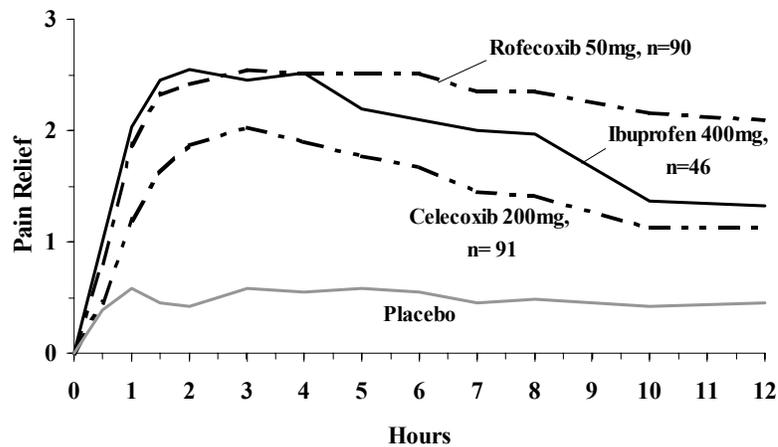
- Ibuprofen 400 mg is significantly more efficacious than both aspirin 650 mg^{2,10} and acetaminophen 1000 mg¹¹ (Figures 1-2); its benefit is even more impressive in subjects with severe baseline pain¹²;
- Ibuprofen 400 mg is significantly superior to 1000 mg of acetaminophen while the 200 mg dose of ibuprofen has been shown to be equianalgesic³ (Figure 2);
- Ibuprofen 400 mg has been shown to provide significantly better efficacy than acetaminophen combined with codeine,^{13,14} and to provide comparable efficacy to other commonly used narcotic combinations:^{15,16}

- Ibuprofen 400 mg is comparable to rofecoxib 50 mg and has statistically significant and clinically superior efficacy compared to celecoxib 200 mg over the first 4-6 hours^{17,18} (Figure 5);
- Ibuprofen is unsurpassed by other NSAIDs (diclofenac,¹⁹ ketoprofen,²⁰ naproxen sodium^{21,22}) at their indicated analgesic doses.

In addition to the aforementioned trials in the oral surgery pain model, ibuprofen 200-400 mg has also been shown to be highly effective, and significantly superior to aspirin or acetaminophen in headache pain,^{23,24} sore throat,²⁵ sports injuries²⁶ and episiotomy pain.^{27,28}

Figure 5

Malmstrom et al., 1999
Oral Surgery (impaction)



Ibuprofen has been proven efficacious for a broad variety of painful conditions. It has a positive dose-response with a higher analgesic ceiling than either aspirin or acetaminophen. These characteristics allow for a flexible dosing regimen so that drug exposure can be titrated to the intensity and duration of the pain being treated.

III. Ibuprofen Safety

The safety data that have been generated since ibuprofen became available as an OTC analgesic in 1984 are derived from the following sources:

- Clinical trials conducted by Wyeth Consumer Healthcare (WCH);
- Published literature on the safety and efficacy of ibuprofen;
- Post-marketing surveillance databases;
- Exposure data from the American Association of Poison Control Centers.

It is important to note that the post-marketing safety surveillance database for OTC ibuprofen is quite extensive. Given ibuprofen's NDA status, all adverse drug experience reports received by the manufacturer since its approval OTC in 1984 have been submitted to FDA. In contrast, because aspirin and acetaminophen are monographed drugs, their manufacturers are not required to submit adverse event reports to the Agency.

A. Gastrointestinal Safety

At the time of the deliberations that led to the switch of ibuprofen from prescription to OTC status in 1984, the gastrointestinal (GI) safety of the drug was thoroughly reviewed and has remained under close surveillance ever since. There is a vast body of evidence, including data from controlled clinical trials, epidemiology studies, and actual consumer use spanning 18 years, which show that: a) while there is an increased risk of experiencing serious GI events when ibuprofen is taken at prescription doses on a chronic basis, ibuprofen has the most favorable GI safety profile of all prescription NSAIDs; b) when administered at OTC doses and for a short duration for use (i.e., up to 10 days), the GI safety profile of ibuprofen is even more favorable, with an extremely low risk of causing serious gastrointestinal events, and c) despite close surveillance, no new GI adverse effect trends have been identified since ibuprofen became available for OTC use in 1984.

Controlled Clinical Studies

The safety of ibuprofen administered at OTC doses (up to 1200 mg/day) for up to a maximum of 10 days has recently been studied in three prospective, randomized, double-blind clinical trials. While these studies had limited power to detect rare, significant adverse events, they were useful in evaluating the incidence of more

frequently occurring, non-serious side effects associated with NSAID use, such as “GI upset”. The designs of these studies are summarized in Table 1.

The PAIN study, which was conducted by Moore, et al., was designed to compare the safety of ibuprofen (1200 mg/day), with aspirin (3000 mg/day) and acetaminophen (3000 mg/day) in the treatment of acute pain in 8677 patients for up to seven days.²⁹

In that trial:

- Ibuprofen was associated with a significantly lower rate of GI complaints compared to both aspirin and acetaminophen (Figure 1);
- There were no serious GI events with ibuprofen, compared to an incidence rate of 0.14% for aspirin, and 0.1% for acetaminophen;
- The rate of discontinuation was low for all three treatments, and lowest for ibuprofen (Figure 2).

WCH has conducted two Multiple Use Safety and Efficacy Studies (MUST I and II), which evaluated the safety of ibuprofen administered at the maximum daily OTC dose (1200 mg/day) and duration for use (10 consecutive days) in subjects representative of the OTC analgesic consumer population.^{30,31} MUST study I compared the GI safety profile of OTC ibuprofen to placebo in over 1200 subjects, while MUST study II compared OTC ibuprofen to celecoxib 200 mg/day, as well as placebo, and enrolled over 2200 subjects. As an indirect measure of blood loss, fecal samples were collected in both studies and analyzed for occult blood. The results from these trials are as follows:

- The incidence of GI symptoms for ibuprofen was no different from placebo in both studies (Figure 6). In addition, the incidence of GI symptoms for celecoxib was similar to that of ibuprofen (MUST II).
- There was one serious GI event in each study;
 - in MUST I, there was one report of GI ulcer, bleeding and diverticulitis with ibuprofen. These events were considered unrelated to ibuprofen because it was subsequently learned that the subject did not take any study medication;

- in MUST II, there was one report of diverticulitis in a subject who had received ibuprofen during the trial. The event was considered unrelated to the drug since it occurred 7 days after the completion of the study;
- In both trials, the incidence of subject withdrawal due to an adverse event was low, and there were no significant differences between treatment groups (Figure 7);
- In both studies, only 0.5 – 1.4% of the subjects tested positive for fecal occult blood. There were no significant differences among the treatments.

Table 1 Overview of Multiple Dose Clinical Trials Evaluating OTC Ibuprofen Safety

Trial	Population	Design	Treatment Groups	Duration	Sample Size
PAIN Study ²⁹	Patients 18-75 requiring short term treatment for mild to moderate pain	Randomized, double-blind, parallel group, outpatient, multiple dose	ASA 500 mg; up to 3000mg/day	1-7 days	2753
			APAP 500 mg; up to 3000 mg/day		2743
			IBU 200 mg; up to 1200 mg/day		2737
MUST Study I ³⁰	Consumers of OTC analgesics	Randomized, double-blind, parallel group, outpatient, multiple dose	IBU tablets 1200 mg/day	10 days	415
			IBU liquigels 1200 mg/day		418
			PBO		413
MUST Study II ³¹	Consumers of OTC analgesics	Randomized, double-blind, parallel group, outpatient, multiple dose	IBU 1200 mg/day	10 days	908
			CBX 200 mg/day		891
			PBO		450

ASA = Aspirin; APAP = Acetaminophen; IBU = Ibuprofen; CBX = Celecoxib

Figure 6

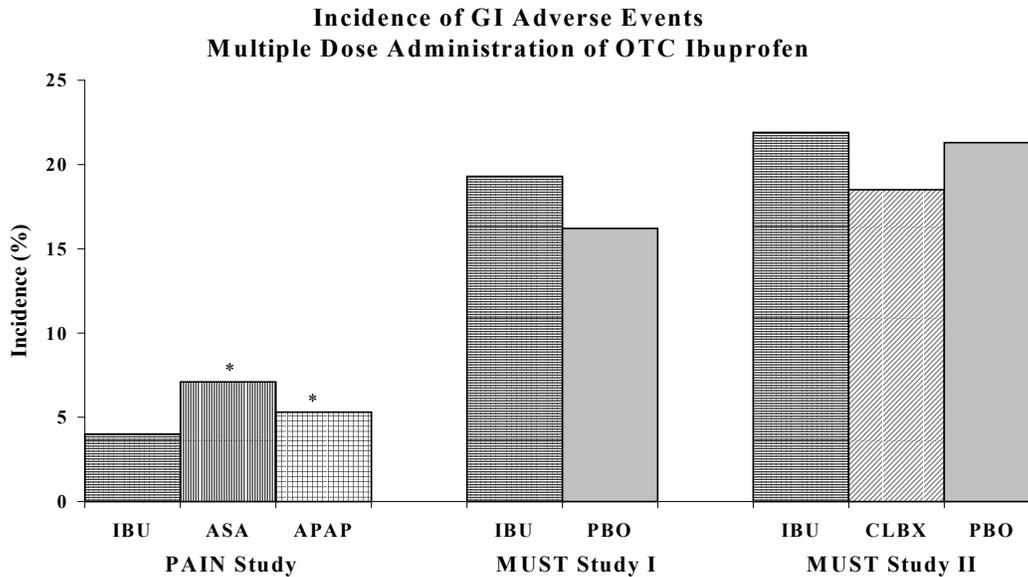
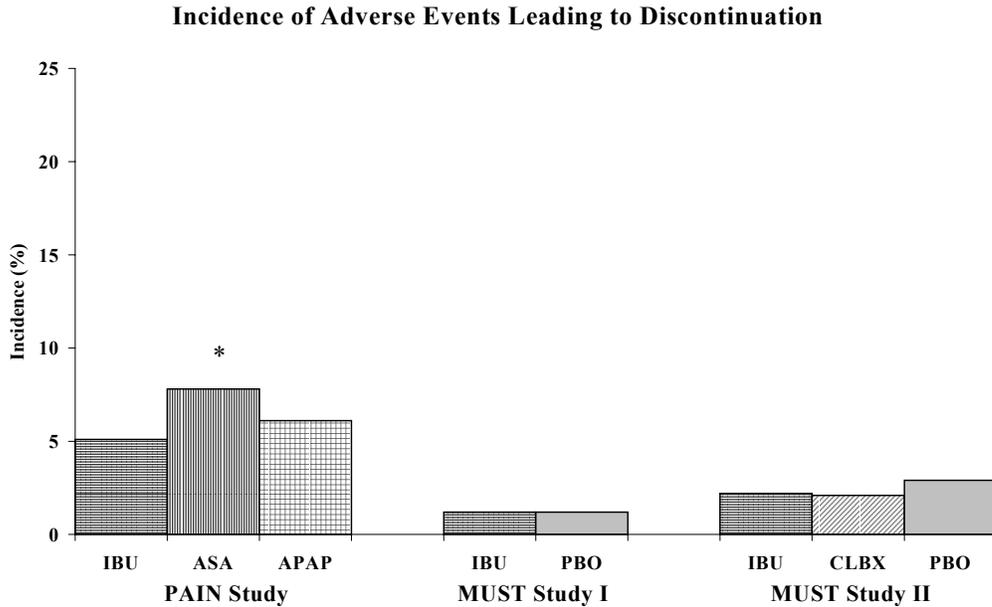


Figure 7



*Significantly worse compared to IBU

Taken together, the PAIN and MUST studies show that the GI tolerability of low dose, short term ibuprofen use is very favorable. While the MUST Studies demonstrated that GI tolerability was comparable to placebo, the PAIN study indicated that the GI tolerability of ibuprofen was superior to aspirin, and comparable to acetaminophen. Although OTC ibuprofen is perceived by the medical community (perhaps due to their experience with prescription NSAIDs) to cause GI upset, these studies clearly demonstrate that this is not the case. Although individually, these trials had limited power to evaluate the incidence of serious events because of their limited sample sizes, taken together, with over 4400 subjects receiving ibuprofen, they do provide supportive data that the incidence of serious GI events with OTC ibuprofen is very rare and there is an absence of occult bleeding.

In addition to ibuprofen's widespread use in adults, it also has a long history of safe use in children. Ibuprofen was originally approved as a prescription drug for children in 1989, and was switched OTC in 1995. In support of its OTC switch, two large scale clinical trials were conducted, the Children's Analgesic Medicine Project (CAMP),³² and the Boston Fever Study.³³ Both studies focused on examining the

potential risk of rare, serious events, including GI bleeding and renal failure in children treated with ibuprofen. In these two studies, over 76,000 of the 114,359 children were treated with ibuprofen, while the remaining received acetaminophen. Both studies demonstrated that there were no significant differences between ibuprofen and acetaminophen in the observed risk of GI bleeding, indicating that the treatment of children with ibuprofen for acute pain and fever is not associated with an increased risk over acetaminophen of serious GI adverse events.

In addition to the clinical trials cited above, ibuprofen has been evaluated in hundreds of other clinical trials. It has been one of the most thoroughly studied drugs on the market today. Accordingly, over the years, there have been four meta-analyses of the safety data from numerous single-dose and/or multiple-dose, randomized, double-blind clinical trials evaluating OTC doses of ibuprofen in adults.³⁴⁻³⁷ These evaluations are summarized in Table 2. While there may have been some overlap in the data included in these various analyses, which consisted anywhere from 878 to 3111 ibuprofen-treated patients, they provide additional data indicating that OTC ibuprofen has an excellent safety profile in multiple-dose, as well as single-dose use. The analyses consistently show that OTC doses of ibuprofen have a frequency of GI events similar to placebo, or acetaminophen.

Table 2 Overview of Meta-Analyses of Controlled Clinical Trials to Evaluate the Safety Profile of OTC Ibuprofen

Author	Scope of Analysis	Treatments (sample size)	Results
Furey, et al. ³⁴ (1992)	15 double-blind, randomized, placebo controlled, single dose trials	IBU 200–400 mg (n=878) APAP 650-1000 mg (n=849) PBO (n=852)	Incidence of GI AEs was comparable for all 3 treatments IBU=0.9% APAP=1.1% PBO=0.9% No serious GI AEs reported No renal AEs reported
DeArmond, et al. ³⁵ (1995)	19 double-blind, randomized, single-dose and multiple-dose trials which included IBU as comparator	IBU 200-400 mg (n=1574) PBO (n=1061)	Most Common GI AE: Nausea IBU=2.2% PBO=2.1% No serious GI or Renal AEs reported
Rainsford, et al. ³⁶ (1997)	96 double-blind, randomized, single-dose and multiple dose trials	IBU (n=3111) APAP (n=5958)	Incidence of GI AEs with IBU was comparable to APAP No serious GI or renal AEs reported
Kellstein, et al. ³⁷ (1999)	8 randomized, multiple-dose, placebo controlled multiple-dose trials	IBU 800-1200 mg/day (n=1094) PBO (n=1093)	Incidence of GI AEs with IBU was comparable to PBO IBU=12.1% PBO=11.0% No renal AEs reported

IBU = Ibuprofen; APAP = Acetaminophen; PBO = Placebo

Epidemiology Studies

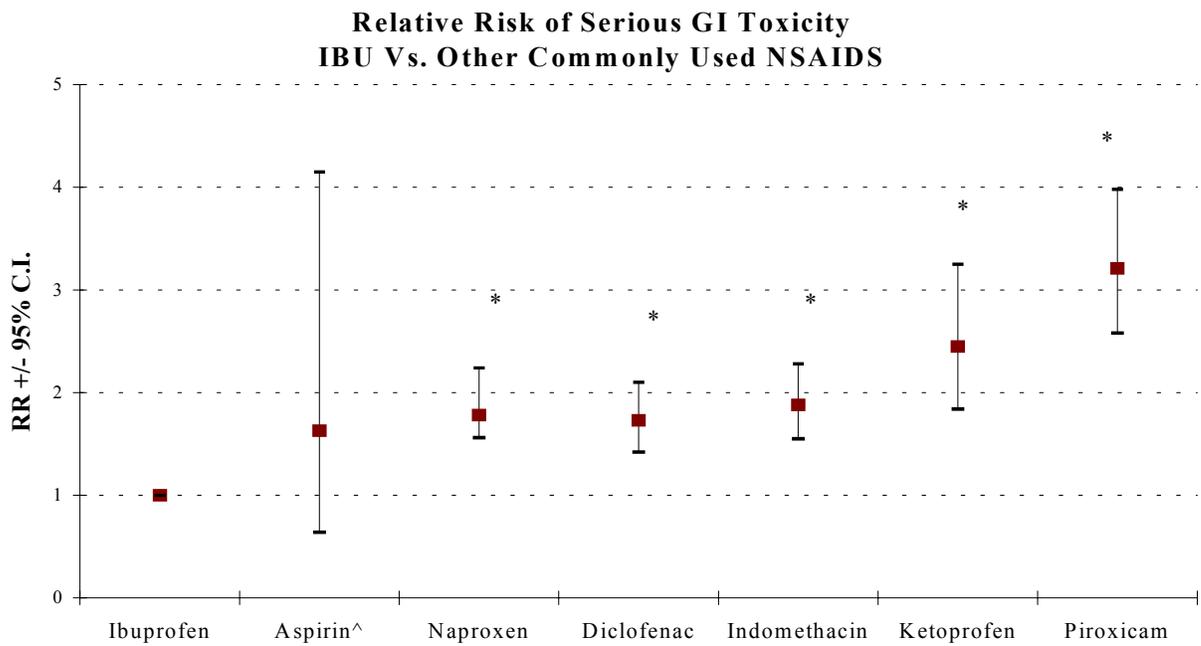
Because of their widespread use, there have been many epidemiological studies evaluating the relationship between NSAIDs and serious GI events. Henry, et. al. recently completed a comprehensive meta-analysis of controlled epidemiological studies which used **prescription** drug databases to evaluate the relationship between NSAID use and hospital admissions for serious GI events.³⁸ The analyses included 36 case control trials and 8 controlled cohort studies which had been completed through June 2001.

- Sixteen of the case control studies included ibuprofen. The pooled relative risk of developing a serious GI event for ibuprofen in these studies was 1.81 (95% CI = 1.34, 2.43);
- Nine of the 16 studies had relative risk 95% confidence intervals which included unity;
- Figure 8 presents the results of pooling the studies which compared ibuprofen to a specific NSAID. Using ibuprofen as the reference, naproxen, diclofenac,

indomethacin, ketoprofen, and piroxicam all had a significantly higher relative risk than ibuprofen. Although aspirin was shown to be no different from ibuprofen in this analysis, it should be noted that in the majority of studies, aspirin was taken in low doses for cardioprotection;

- Seven studies evaluated the relative risks associated with low doses and high doses of prescription NSAIDs. Five of these studies evaluated ibuprofen. The pooled results from these 5 trials are presented in Figure 9 and indicate that the relative risk for ibuprofen at lower doses, (defined as ≤ 1500 mg in some studies, and ≤ 1800 mg in others; RR =1.42, 95% CI 0.93, 2.15) is significantly reduced compared to higher ibuprofen doses (defined in some studies as ≥ 1500 mg and in others as ≥ 1800 mg; RR = 4.40, 95% CI 2.79, 6.92). These results showed that lower doses of ibuprofen were not associated with an increased risks of serious GI adverse events, which is especially impressive since:
 - The “low doses” of ibuprofen defined in these studies (≤ 1500 mg/day in some studies, and ≤ 1800 mg/day in others) were higher than the OTC dose of 1200 mg/day;
 - These studies evaluated data from prescription databases, which probably included patients who were chronically taking ibuprofen, and who were also likely to have had confounding underlying disease.

Figure 8



Studies in meta-analysis†

11

18

13

18

13

15

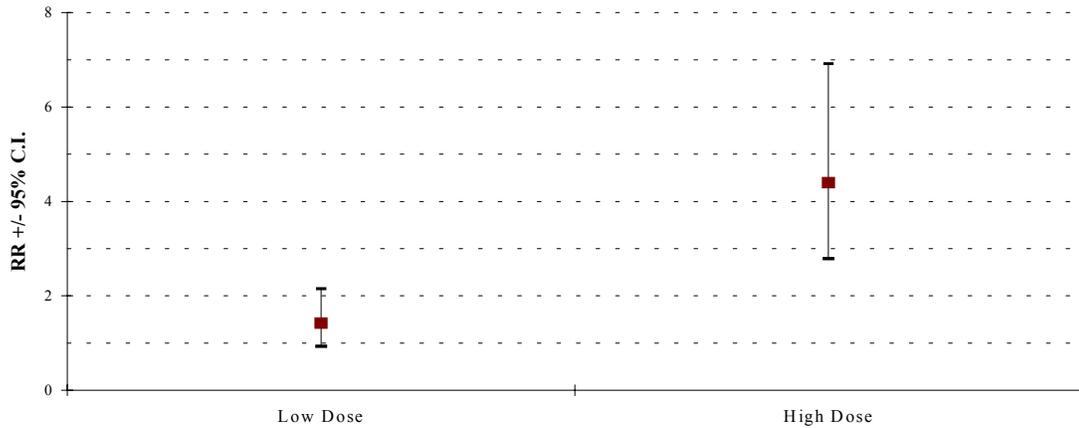
† Each Comparison was based on a meta analyses of controlled epidemiological studies which simultaneously evaluated the drug with IBU

^ Majority of aspirin use was as intermittent low-doses in analgesia, or low-dose prophylaxis in CV disease

*Significantly worse than ibuprofen at 0.05 level

Figure 9

Relative Risk# of Serious GI Toxicity with Ibuprofen Low Vs High Dose



RR Vs non-use of any NSAID, based on a meta analysis of studies which provided data on both "Low" and "High" dose use of Ibuprofen. "Low" dose as defined within each study, and varied as ≤ 1500 mg, and ≤ 1800 mg

Using a prescription database known as ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System), Singh, et al. concluded that there is an overall increased risk of developing serious GI toxicity with OTC doses of NSAIDs.³⁹ Even within this dataset based on chronic prescription use in patients with significant underlying disease, ibuprofen was reported to have a rate of GI hospitalization (per 100 patient years) of 0.65, with the 95% confidence interval included zero (95% CI 0.0, 1.38).

Blot and McLaughlin published an analysis of the American College of Gastroenterology (ACG) bleeding registry to evaluate the potential risks of gastrointestinal bleeding associated with OTC NSAIDs. The ACG bleeding registry was generated in 1995 by having members of the ACG participate in a mail survey, where they provided information in a non-randomized, non-blinded manner on up to 10 patients with GI bleeding and 10 procedure-matched patients without GI bleeding.⁴⁰ Of those patients in the registry who developed GI bleeding, 10.1% reported taking OTC doses of ibuprofen, compared to 5.8% of controls. The odds ratios were related to the dose of ibuprofen as follows: ≤ 600 mg per day had a ratio of 1.8 (95% CI 0.8, 4.1), while ≤ 1200 mg per day had a ratio of 3.5 (95% CI 1.2, 10.7). The relevance of these data to true OTC use of ibuprofen is unknown, since critical information regarding

duration of use was not collected, and since the survey was conducted in an uncontrolled, non-randomized, non-blinded manner.

To WCH's knowledge, there are no epidemiology studies which have specifically evaluated the relative risk of OTC doses of ibuprofen administered under OTC conditions (i.e., ≤ 10 days). This is probably because most databases do not track use of OTC products; therefore, the data are not accessible. However, a case-cohort study by Strom et al, was specifically designed to estimate the relative risk of GI bleeding associated with OTC doses of naproxen sodium and ibuprofen by evaluating events which occurred within the first 2 weeks of dosing among those Medicaid patients whose average daily dose was ≤ 600 mg/day of naproxen sodium or ≤ 1200 mg/day of ibuprofen.⁴¹

- The incidence of GI bleeding associated with ibuprofen was 0.012%, and 0.026% for naproxen sodium;
- Compared to ibuprofen, the adjusted relative risk for those using naproxen sodium was significantly higher, 2.0 (95% CI 1.1, 3.8).

It should be noted that the absolute risk for serious GI bleeding was extremely low for both drugs.

In addition to the Strom study, the effect of the increased availability of OTC NSAIDs on the hospitalization and mortality rates from gastrointestinal bleeding and peptic ulcer disease was evaluated by Lewis, et al.⁴² As presented in the table below, the hospitalization and mortality rates due to these conditions have not increased concurrently with the increasing sale of NSAIDs over the years.

Table 3 Correlations Between NSAID Sale and Rate of Hospitalization and Mortality for Peptic Ulcer Disease and GI Bleeding

	Mortality from Peptic Ulcer Disease	Hospitalization from Peptic Ulcer Disease	Mortality from GI Bleeding	Hospitalization from GI Bleeding -
NSAIDs	-0.17, p=0.65	0.14, p=0.38	-0.67, p=0.96	-0.67, p=0.96
Aspirin	-0.31, p=0.77	0.33, p=0.21	-0.62, p=0.94	-0.74, p=0.98

NSAIDs + Aspirin	-0.24, p=0.71	0.31, p=0.23	-0.81, p=0.99	-0.88, p=0.99
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In the aggregate, the vast amount of epidemiological data indicates that ibuprofen is quite safe, even at prescription doses. More importantly, from the epidemiological data that approximates OTC use, it appears that the incremental risk of serious GI events from OTC ibuprofen is extremely low relative to the background incidence of GI bleeds.

Ibuprofen GI Safety Surveillance Data

Data from FDA's spontaneous reporting system for all single ingredient ibuprofen products from the period May 1984 through March 2002 have been reviewed. The data presented here include only the reports of adverse events associated with the administration of ibuprofen for ten days or less, at doses of 1200 mg/day or less, and in subjects 12 years of age or older, with no use of concomitant drugs reported (reports where any information was missing were also included). Note: The Agency's review of ibuprofen GI safety surveillance data (provided to the public on August 23, 2002) was limited to the cases reported to FDA from January 1, 1998 through December 31, 2001.

Over the 18-year period, a total of 5042 adverse event reports have been received for ibuprofen. Of these, 15.2% (n = 768) were serious, and of the serious reports, 42% (n = 324) possessed at least one GI system term (~ 18 serious GI events/year). Clinically significant reports, such as GI bleeding and perforation (n = 71) were infrequent over the 18-year reporting period. Of the 324 serious GI reports received during this 18-year period, an outcome of death was noted in four, presumably due to GI bleeding. Three of those who died were between the ages of 72-94. The age of the fourth individual was not provided. One patient had been taking 1200 mg/day of ibuprofen for an unknown period at the time of death. Dosing information for the other three deaths was not available.

When data including those who took concomitant medication were examined, there was a total of 62 deaths involving GI bleeding (including the 4 patients cited above).

Twenty-five of these patients had been taking ibuprofen 1200 mg/day or less, 19 males and 6 females. Most of these patients (n=18) were ≥ 65 years of age, and seven had been taking aspirin concomitantly. For the remaining 37 cases, ibuprofen dosing information was not provided. Nine of these patients were male, 15 were female, and the gender of 13 patients was not provided. Of the 25 patients whose age was provided, 20 were ≥ 65 years old. Twelve of the 37 patients had also been taking low dose aspirin and/or another NSAID (in addition to ibuprofen).

Two decades of postmarketing experience in the United States have established that the reporting frequency of serious GI events has remained consistently low during this time, suggesting that OTC ibuprofen is well tolerated in the general population.

B. Renal Safety

All NSAIDs can produce a variety of adverse effects on the kidney. While there is little threat of renal insult with NSAIDs in normal, healthy individuals, risks may be increased in the elderly, in those who are dehydrated, and in those with underlying renal disease. The risk of certain types of renal toxicity may increase with the dose and duration of NSAID use.

Almost three decades of postmarketing experience with prescription-strength ibuprofen in the United States and worldwide, during which over 100 billion doses have been administered, has shown the [reporting] frequency of renal side effects to be low. Post marketing experience with non-prescription ibuprofen confirms its safety in the general population. Safety data from controlled clinical trials add further assurance that non-prescription doses of ibuprofen are well tolerated by the kidneys.

The foregoing publicly-available information has been extracted from the original Citizen's Petition to request monograph status for ibuprofen (July 1997), and two updates (through 2001). The published OTC experience of ibuprofen during the past 18 years is consistent with a very safe profile with respect to the renal system. Despite the National Kidney Foundation's first consensus statement published in 1984, a more

recent statement in 1996, and a public FDA feedback meeting on the subject, the dire renal consequences which were forecasted with the OTC availability and use of ibuprofen have not materialized. When used as directed, the potential of OTC ibuprofen to cause renal problems is extremely low.

Controlled Clinical Trials

Prescription Doses

As shown in the following table, several studies indicate that under prescription use, ibuprofen is not commonly associated with adverse renal function in those without underlying renal disease. These findings suggest that, even at higher doses and longer duration of use, ibuprofen therapy is not commonly associated with adverse renal effects.

Table 4. Controlled Clinical Trials with Ibuprofen in Patients without known Underlying Renal Disease

Author/Year	No. Patients	Daily Dose	Duration	Outcome
Bradley, 1991 ⁴³	62	1200 mg	4 weeks	No significant effect on renal function
Cummings 1988 ⁴⁴	52 (63-87 years)	1600 mg	6 weeks	No significant effect on renal function
Fox, 1984 ⁴⁵	8412	Rx doses	in-patients = 12 days out-patients ≥ 5 Rx/yr	No significant effect on renal function
Bonney, 1986 ⁴⁶	182	1200-2400 mg	Up to 1 year	2 reports of elevated BUN or creatinine: clinically asymptomatic

OTC Doses

As previously discussed under the GI Safety section of this document, the safety of ibuprofen administered at OTC doses (up to 1200 mg/day) for up to a maximum of 10 days was studied in three independent, prospective, randomized, double-blind clinical trials (the PAIN Study, MUST I and MUST II Studies).²⁹⁻³¹ While these studies individually had limited power to detect rare, significant adverse events, taken together, 4478 individuals received ibuprofen, without a single incident of a serious renal event. Similarly, in the two large scale studies that were conducted in children (CAMP and the Boston Fever Study), where over 76,000 children received ibuprofen, there was no occurrence of acute renal failure.^{32,33}

In addition, there have been several studies conducted on the safety of OTC ibuprofen in those at risk for developing renal effects. These studies are presented in Table 5 and show that renal effects, if any, were reversible after discontinuation of drug.

Table 5. Controlled Studies Evaluating Renal Safety of OTC Ibuprofen in At-Risk Individuals

Author/ Year	Age/Sex or # of patients	Daily Dose	Duration	Comments/Outcome
Stosic 1995 ⁴⁷	55 patients with hx of reduced renal function	1200 mg	7 days	Ibuprofen caused a significant decrease in GFR and renal plasma flow.
Furey 1993 ⁴⁸	8 elderly patients	1200 mg	7 days	No change in renal function.
Farquhar 1999 ⁴⁹	12 healthy, exercised induced kidney stress	1200 mg	1 day	Ibuprofen had a small, but statistically significant effect on glomerular filtration rate compared to placebo (73.5 ± 5 vs 82 ± 5 mL/min, respectively).
Sheiner 1994 ⁵⁰	18/F	4 tablets (unknown)	2 days	Reduced creatinine clearance which reversed after drug was discontinued
	17/F	1200 mg	1 day	Elevated creatinine, oliguric. Reversed after ibuprofen was discontinued.

Meta Analyses of Controlled Clinical trials

Prescription Doses

A comparison of adverse renovascular experiences among 8460 osteoarthritis patients treated with the selective COX-2 inhibitor rofecoxib 25-12.5 mg/day or ibuprofen 2400 mg/day (n=1902) established that rofecoxib was generally similar to

ibuprofen.⁵¹ In that trial, the relative rates of renal events per 100 patient months of exposure (with 95% CI) in those who received ibuprofen were as follows:

- Acute renal failure: 0.1 (0.0, 0.2)
- Elevated serum creatinine: 0.5 (0.2, 0.8)
- Incidence of hypertension AEs: 1.3 (0.8,1.8)
- Incidence of lower extremity edema AEs: 1.7 (1.1, 2.3)

A recently published meta analysis of 14 trials by the Cochrane group reviewed the effect of NSAIDs on post-operative renal function in normal adults. The authors concluded that NSAIDs should not be withheld from adults with normal pre-operative renal function because of concerns about post-operative renal impairment.⁵²

OTC Doses

As was discussed under the GI Safety section of this document, there have been 4 meta-analyses of the safety data from numerous single-dose and/or multiple-dose, randomized, double-blind clinical trials evaluating OTC doses of ibuprofen in adults.³⁴⁻³⁷ These analyses are summarized in Table 2. There were no instances of serious renal effects reported in any of these analyses, providing additional data indicating that OTC ibuprofen has an excellent renal safety profile in short term, multiple-dose, as well as single-dose use.

Case Reports

To WCH's knowledge, the literature contains very few case reports of renal dysfunction associated with ibuprofen administered at OTC dosage and duration in those without underlying renal disease.

As presented in Table 6, there are 7 case reports of renal dysfunction in patients without underlying renal illness who had taken ibuprofen, but the dosage that had been taken was either higher or longer than the OTC dose. Following appropriate medical management, normal renal function was restored in all of these patients.

Table 6. Case Reports of Renal Dysfunction in Those Without Underlying Disease Who Had Taken Ibuprofen

Author/Year	Age/Sex	Dose	Duration	Comments/Outcome
Elasser, 1998 ⁵³	19/F	1600 mg/day	6 days	Elevated BUN, creatinine. Decreased urine output. Improvement seen after d/c ibuprofen, spironolactone.
Johnson, 1995 ⁵⁴	22/F	1200 mg (heavy alcohol intake the evening prior)	single dose	Elevated BUN, creatinine. Acute renal failure was reversed.
Moss, 1986 ⁵⁵	43/M	600 mg/day	2 days	Acute renal failure treated with hemodialysis, prednisone.
Marasco, 1987 ⁵⁶	45/M	800 mg/day	~ 5 weeks	Tubulointerstitial nephritis reversed after d/c ibuprofen with hemodialysis, methylprednisolone tx.
McIntire, 1993 ⁵⁷	12/F	600 mg, then 200 mg q6h	Unknown	Acute renal failure. Reversed.
Wattad, 1994 ⁵⁸	14/F	600 mg	Single dose	Nonoliguric acute renal failure. Reversed after prednisone treatment.
Fernando, 1994 ⁵⁹	76/M	4 tablets (unknown)	Single dose	Acute anuric renal failure. Recovered after hemodialysis
		Topical	Single dose	Acute anuric renal failure. Recovered with hemodialysis and methylprednisolone treatments

Table 7 presents two summaries of case reports and two individual case reports wherein a total of 14 patients with underlying renal disease experienced various additional renal functional abnormalities and changes associated with OTC doses of ibuprofen.

Table 7. Case Reports of Adverse Renal Effects with OTC Ibuprofen in Those With Underlying Renal Disease

Author/Year	Age/Sex or # of patients	Daily Dose	Duration	Comments/Outcome
Spierto 1992 ⁶⁰	73/M	600mg	1 week	Acute renal failure with digoxin toxicity. Reversed after discontinuation of drug.
Atkinson 1986 ⁶¹	22/F	1200 mg	6 days	Elevated creatinine, acute renal failure. Reversed after ibuprofen was discontinued.
Whelton 1990 ⁶²	2 patients	2400 mg	11 days	Elevated creatinine levels, acute renal failure, asymptomatic, reversed after ibuprofen was discontinued.
Ciabottoni 1984 ⁶³	10 patients	1200 mg	1 week	Elevated mean creatinine, decreased mean creatinine clearance. Reversed after ibuprofen was discontinued.

Epidemiology Studies

Many of the epidemiological studies report on NSAIDs as a class and do not report specific data for ibuprofen. Studies that specifically mention ibuprofen generally provide little information on dose or duration of use. For example, Sandler, et al. and Perneger, et al. included NSAIDs in their case control studies to examine renal dysfunction and end-stage renal disease, respectively.^{64,65} Neither study provided specific data on dose or duration of ibuprofen use.

A study by Rexrode, et al. examined whether analgesic use is associated with a risk of renal dysfunction.⁶⁶ This cohort study included 11,032 previously healthy men who provided blood samples and a self-report of analgesic consumption. The main outcome measures during this 14-year study of men 40-84 years were elevated creatinine levels (≥ 1.5 mg/dL), a reduced creatinine clearance (≤ 55 mL/min), and self-reported use of acetaminophen, aspirin, and NSAIDs (never [< 12 pills], 12-1499 pills, 1500-2499 pills, and ≥ 2500 pills). Mean creatinine levels and clearance were similar between the groups that used analgesics and those who did not, even in use > 2500 pills. Multivariate analysis (adjusted for age, body mass, history of hypertension, elevated cholesterol, diabetes, cardiovascular disease, physical activity, use of other analgesics) indicated that the relative risks of elevated creatinine levels associated with intake of ≥ 2500 pills were 0.83 (95% C.I. 0.50-1.39) for acetaminophen, 0.98 (95% C.I. 0.53-1.81) for aspirin, and 1.07 (95% C.I. 0.71-1.64) for other NSAIDs. No association was observed between analgesic use and reduced creatinine clearance. The authors concluded that the moderate use of analgesics in a cohort of initially healthy men was not associated with increased risk of renal dysfunction.

Griffin, et al., reviewed the records of 1,799 patients ≥ 65 years old enrolled in the Tennessee Medicaid program from 1987-1991 who had acute renal failure.⁶⁷ Of the 1,799 patients, 18.1% were current users of NSAIDs. Ibuprofen accounted for 35% of the NSAID users. The associated risk of acute renal failure in ibuprofen users was evidenced by increasing odds ratios by dose ≤ 1200 mg (0.94), > 1200 mg- ≤ 2400 mg (1.89), > 2400 mg (2.32).

Murray, et al. conducted a cohort study of 1908 prescription ibuprofen users and 3933 acetaminophen users from the medical records system of Indiana University Hospital during

1975-1986.⁶⁸ The authors included a population with multiple concomitant medical problems in an attempt to identify subgroups who might be at increased risk. Blood creatinine levels >20 mg/L developed in 0.9% of the group receiving prescription ibuprofen. There was no significant difference in the incidence of renal impairment between acetaminophen and ibuprofen users except in those ≥ 65 years of age (relative risk = 1.3 in ibuprofen users, 95% C.I.= 1.1-1.7).

Radford conducted a retrospective chart review of the Mayo Clinic records for the years 1975-1995 to investigate the frequency of membranous nephropathy associated with NSAID use.⁶⁹ Of 125 patients identified with the early stages of this condition, the three that were taking ibuprofen had a duration of use from one to nine months, which far exceeds the recommended duration of OTC use.

Pospishil studied the renal biopsies of previously normal patients who developed renal complications after treatment with NSAIDs including OTC ibuprofen.⁷⁰ While information on dosages was not provided, the authors noted that the patients who developed renal symptoms had, in general, used NSAIDs for prolonged periods of time, ranging from 3 months to seven years.

Safety Surveillance Data

As mentioned previously, data from FDA's spontaneous reporting system for all single ingredient ibuprofen products from the period May 1984 through March 2002 have been reviewed. The data presented here include only the reports of adverse events associated with the administration of ibuprofen for ten days or less, at doses of 1200 mg/day or less, and in subjects 12 years of age or older, with no use of concomitant drugs reported (reports where any information was missing were also included). Note: The data that was included in the Agency's review of ibuprofen renal safety surveillance data (provided to the public on August 23, 2002) included reports submitted to FDA from May 1984 through August 9, 1999.

Of a total of 768 serious adverse event reports received in the last 18 years of post marketing surveillance for OTC ibuprofen, 93 contained at least one adverse event term related to the urogenital system. Of these, there were 26 reports of renal failure. This represents less than two cases reported each year during the OTC availability of ibuprofen, an extremely low reporting frequency that supports the adequacy of the current labeling. Additionally, none of these renal events resulted in death during this time period.

When data including those who took concomitant medication were examined, there were 10 deaths involving renal failure, seven females and three males. Six of the individuals were ≥ 68 years of age, and six were taking at least three other medications (in addition to ibuprofen), at the time of death. Given the limited amount of information available, it is not clear whether renal failure was a pre-treatment event, whether it was related to taking the other medications, related to another medical condition, or related to taking ibuprofen.

C. Safety in Overdose

At the time ibuprofen was approved for OTC use, it was generally recognized that it posed significantly less risk than either acetaminophen or aspirin with respect to overdose. As is evident by data collected and reported by the American Association of Poison Control Centers (AAPCC) from 1987 through 2000, this continues to be the case. Ibuprofen exposures have resulted in the less severe outcomes, and fewer deaths, compared to aspirin and acetaminophen. During this timeframe, there have been only 49 fatalities from 528,396 reports of ibuprofen overdose (a rate of 0.009%), compared to 769 fatalities resulting from 978,014 reports of acetaminophen overdose (a rate of 0.079%) and 576 fatalities resulting from 221,356 reports of aspirin overdose (a rate of 0.26%).

IV. Development of Labeling for OTC Ibuprofen

As previously mentioned, the labeling for all prescription NSAIDs includes detailed warnings about GI and renal toxicity. As the risk of these toxicities is dependent upon the drug, dose, and duration of use, ibuprofen was switched from prescription to OTC status based on:

- its favorable safety profile at prescription doses;

- the proposed maximum daily OTC dose of 1200 mg per day was less than one half of the approved maximum daily prescription dose (3200 mg), which was expected to pose minimal risks to consumers;
- the approved single dose of 200-400 mg was shown to be a very effective analgesic and was designed to allow for flexibility in dosing where necessary

While drugs that are granted OTC status are felt to pose minimal safety risks to consumers, no drug is entirely safe. Therefore, the labeling for OTC drugs should clearly communicate the intended target population, indications for treatment, dosing instructions, populations at risk, potential harmful outcomes, and what to do should there be a harmful outcome. At the same time, labels should not be so overloaded with information as to dilute the information consumers need to read.

Labeling for prescription products (including NSAIDs) is lengthy and very detailed because it is primarily designed to provide the physician or learned intermediary with as much information as possible about the drug so that he/she can select the appropriate drug and provide appropriate counsel to the patient. On the other hand, labeling for OTC products is intended for the consumer. The current labeling for OTC ibuprofen is based on data from a study designed by FDA. During the approval process, there was lengthy consideration by the Agency of whether potential consumer confusion and associated problems might occur with the introduction of this entirely new OTC analgesic. FDA took the unusual step of forming a multi-disciplinary internal task force to advise on the development of labeling for OTC ibuprofen. During the group's deliberations, it became evident that there were divergent views about how to most effectively communicate the warnings and precautions to consumers. Two different labels were developed reflecting the disparate views of the task force. One version was more general and indicated in broad terms when a consumer should consult a physician. The second version was more specific and listed nearly all the diseases and conditions that would require a user to consult a physician before use. Following a protocol developed by the Agency, the labels were tested in a mall intercept study involving 300 consumers from 13 locations throughout the US.

Results of the study were discussed in the Medical Officer's Review for the sponsor NDAs. Interestingly, many of the more general warning statements were better understood by consumers than the more specific ones. Subjects receiving the more specific label were more likely to self-diagnose their medical condition and determine the suitability for using ibuprofen without consulting a physician. However, those seeing the more general version were more likely to consult their doctor as a source of information about using the product rather than make a decision about taking the drug on their own. Based on the results of the research, the task force arrived at labeling they believed combined the better portions of each of the versions. As agreed to with the Agency, Sponsors provided educational campaigns for consumers and health professionals to make sure that aspirin sensitive individuals were suitably informed about OTC ibuprofen. Sponsors also worked with the Agency to create educational materials to promote safe and effective use of OTC ibuprofen.

Over the past 18 years, the labeling for OTC ibuprofen has been revised to include several new warnings. In 1986 when generic ibuprofen products came on the market, a warning was added to state clearly that the product should not be used with any other ibuprofen-containing product. In 1990, the Agency required sponsors to capitalize the statement "IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT." This was implemented as a precautionary step by the Agency and, to the best of WCH's knowledge, was not in response to a specific incident or complaints from health care professionals.

In 1998, the Agency amended its regulations to require a revised allergy warning for NSAID drug products. OTC ibuprofen had included a warning for "ASPIRIN SENSITIVE PATIENTS" since the time of approval in 1984. Under the new regulation, this warning was replaced with the following:

Allergy alert: ibuprofen may cause a severe allergic reaction which may include:

- hives
- facial swelling
- asthma (wheezing)
- shock

Do not use if you have ever had an allergic reaction to any other pain reliever/fever reducer.

Stop use and ask a doctor if an allergic reaction occurs. Seek medical help right away.

Additionally, in 1998, the Agency issued a regulation requiring an organ specific alcohol warning on all OTC analgesic products. The following warning was added to OTC ibuprofen labeling:

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

In May 2002, the drug facts rulemaking became effective for many OTC drug products. This rulemaking requires a bulleted format and a standard order or presentation of information on the label for all OTC products. Wyeth Consumer Healthcare has revised Advil labeling to the required format. The “Warnings” and “Directions for Use” sections of the current label are presented below, and include specific statements that aid the consumer in using the product safely.

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction which may include:

- hives
- facial swelling
- asthma (wheezing)
- shock

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

Do not use if you have ever had an allergic reaction to any other pain reliever/fever reducer

Ask a doctor before use if you have

- had problems or side effects with any pain reliever/fever reducer
- stomach pain

Ask a doctor or pharmacist before use if you are

- under a doctor’s care for any continuing medical condition
- taking other drugs on a regular basis
- taking another product containing ibuprofen, or any other pain reliever/fever reducer

When using this product take with food or milk if stomach upset occurs

Stop use and ask a doctor if

- an allergic reaction occurs. Seek medical help right away.
- fever gets worse or lasts more than 3 days
- pain gets worse or lasts more than 10 days
- stomach pain occurs with the use of this product
- the painful area is red or swollen
- any new or unexpected symptoms occur

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
- adults: take 1 tablet every 4 to 6 hours while symptoms occur
- if pain or fever does not respond to 1 tablet, 2 tablets may be used, but do not exceed 6 tablets in 24 hours, unless directed by a doctor
- the smallest effective dose should be used
- children: do not give to children under 12 unless directed by a doctor

As previously mentioned, on August 21, 2002, the Agency published a proposal in the Federal Register to amend the tentative final monograph (TFM) for OTC internal analgesic, antipyretic and antirheumatic drugs to include ibuprofen as a generally recognized safe and effective analgesic/antipyretic for OTC use. The Agency based its recommendation on the very favorable safety profile of OTC ibuprofen. Importantly, this safety profile has been generated from ibuprofen's current OTC label. As part of their proposal however, the Agency has recommended the addition of more specific GI and renal warnings to the label as follows:

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction which may include:

- hives
- facial swelling
- asthma (wheezing)
- shock

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

Do not use if you have ever had an allergic reaction to any other pain reliever/fever reducer

Ask a doctor before use if you have

- ~~had~~ problems or serious side effects ~~with any from taking~~ pain relievers/ or fever reducers
- stomach ~~pain~~ problems that last or come back, such as heartburn, upset stomach, or pain
- ulcers
- bleeding problems
- high blood pressure, heart or kidney disease, are taking a diuretic, or are over 65 years of age

Ask a doctor or pharmacist before use if you are

- under a doctor's care for ~~any continuing medical~~ any serious condition
- ~~taking other drugs on a regular basis~~
- taking ~~another~~ any other product ~~that~~ containing ibuprofen, or any other pain reliever/fever reducer
- taking a prescription drug for anticoagulation (blood thinning)
- taking any other drug

When using this product take with food or milk if stomach upset occurs

Stop use and ask a doctor if

- an allergic reaction occurs. Seek medical help right away.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain gets worse or lasts ~~occurs with the use of this product~~
- redness or swelling is present in the painful area ~~is red or swollen~~
- any new ~~or unexpected~~ symptoms appear ~~occur~~

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**
- adults and children 12 years and over: take 1 tablet every 4 to 6 hours while symptoms ~~occur~~ persist
- if pain or fever does not respond to 1 tablet, 2 tablets may be used, ~~but do not~~
- do not exceed 6 tablets in 24 hours, unless directed by a doctor
- the smallest effective dose should be used
- children under 12 years:-ask a doctor do not give to children under 12 unless directed by a doctor

WCH looks forward to working with the Agency to evaluate the current, as well as alternate proposals for improving the label. As with the label comprehension study conducted in 1983 prior to the approval of OTC ibuprofen, greater specificity in the warnings statements may not prove to be as effective as the current more general warnings.

V. Consumer Use Data

As previously mentioned, WCH believes its labeling for OTC ibuprofen has been effective in communicating the appropriate use of this product. In addition to the very favorable safety profile that has been generated since it became available OTC, this is also supported by the following consumer use data which shows that few consumers exceed recommended doses.

In an Attitude and Usage study conducted over a 10-day period in 1996:⁷¹

- the average number of tablets taken per dose was approximately 2
- consumers took ≥ 3 tablets 11% of the time
- the average number of tablets taken per day was 3.6 (~720 mg)
- more than 6 tablets per day (>1200 mg) were taken only 8% of the time.

In a 30-day actual use study conducted in 3094 individuals with a history of using OTC analgesics who were provided with sufficient study medication for 10 days (60 pills):⁷²

- 1.23% took more than 2 ibuprofen tablets per dose
- 7.5% took more than 6 ibuprofen tablets in 24 hours
- 3.72% took ibuprofen for more than 10 days for pain or for more than 3 days for fever

Data from a 2002 Gallup survey indicate that consumers of OTC ibuprofen use an average of 17.1 pills per month.⁷³

- 36% use 1-4 pills/month
- 21% use 5-8 pills/month
- 30% use 9-29 pills/month
- 14% use ≥ 30 pills/month
 - 7.6% use 30- 50 pills/month
 - 4.1% use 51-100 pills/month

- 1.6% use 101-180 pills/month
- 0.8% use > 180 pills/month

Survey data in 2002 indicate that about 65% of Advil's pill volume comes from those 18 to 49 years of age, and 10% from those 65 years or older. The major uses of the brand are: 34% for headache, 21% for arthritis pain, and 16% for muscle aches and pains.

VI. Conclusions

Since ibuprofen's approval for OTC use in 1984, its safety profile has continued to be closely investigated, evaluated and assessed by WCH. While no drug, even if it is OTC, is completely safe, there is a vast amount of data indicating a very low risk of developing serious GI or renal toxicity when OTC ibuprofen is used according to the labeled dosing instructions (i.e. 200-400 mg every 4 – 6 hours, up to 1200 mg per day, for up to 10 days). Because it is critical that consumers follow the labeled dosing instructions for any drug, WCH has worked very closely with FDA in developing the current label for OTC ibuprofen. WCH believes that the long history of safe and effective use of OTC ibuprofen indicates that this labeling has been generally effective in communicating its appropriate use. We have presented consumer behavior data confirming that the vast majority of consumers follow the labeled instructions. While the Agency has recommended that ibuprofen be included in the Tentative Final Monograph, thereby recognizing it as being generally safe and effective, they have also proposed the addition of more specific GI and renal warnings to the label. Although WCH has not had sufficient time to consumer test or evaluate all of the proposed modifications, WCH is fully committed to working with the Agency on improving the label for all OTC analgesic products, including ibuprofen, where necessary. As in the past, WCH strongly believes that any proposed modifications to the label should be adequately tested to ensure the proposed changes actually benefit the consumer.

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