DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Re: Docket No. 2005P-0072/CP1

Dear Dr. Salisbury:

This letter responds to your citizen petition dated February 15, 2005, submitted on behalf of seven petitioners. You request that the Food and Drug Administration (FDA) take the following actions:

1. conduct a risk assessment of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) associated with the use of ibuprofen products;

2. conduct an investigation into manufacturers' withholding of critical safety information regarding the risks of SJS and TEN associated with ibuprofen products; and

3. require manufacturers of ibuprofen to amplify their prescription and over-the-counter (OTC) labeling to adequately warn prescribers, healthcare professionals, and consumers of the risks of SJS and TEN.

For the reasons that follow, your petition is granted in part and denied in part.

I. BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) is a class of drugs that includes ibuprofen products. Ibuprofen products are available by prescription and OTC. Prescription and OTC ibuprofen are indicated for temporary relief of minor aches and pains and reduction of fever. In addition, prescription ibuprofen is indicated for relief of mild to moderate pain; relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis; and treatment of primary dysmenorrhea.

NSAIDs, including ibuprofen, are known to cause SJS and TEN, as reflected in the labeling of NSAIDs, including ibuprofen prescription labeling. While adverse skin reactions to drugs are frequent, serious adverse cutaneous reactions are not. SJS and TEN are within a spectrum of the same disease and are severe drug eruptions. Prompt recognition of the onset of symptoms, such as the appearance of rash or blisters on the

2005P-0072 PAV 1

skin, and withdrawal of the suspected drug can minimize the effects of SJS/TEN and improve prognosis.[1]

In 2005, FDA engaged in a comprehensive review of the risks and benefits, including the risks of SJS and TEN, of all approved NSAID products, including ibuprofen. This comprehensive risk-benefit assessment focused primarily on potential cardiovascular and gastrointestinal safety concerns associated with COX-2 selective and non-selective NSAIDs. On April 6, 2005, FDA issued a press release and public health advisory announcing a series of actions to alert consumers and healthcare practitioners about the risks associated with the use of COX-2 and NSAID products. FDA also posted a Decision Memo entitled "Analysis and Recommendations for Agency Action- COX-2 Selective and Non-selective NSAIDs" (www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf) (Decision Memo). In its Decision Memo, FDA emphasized the public health importance of maintaining a range of options in the NSAID class from which physicians and patients may choose (Decision Memo at 11-13).

The Agency's actions included issuing supplemental request letters to manufacturers of all NSAIDs asking that they make labeling changes to their products. In addition, FDA posted labeling templates for both the prescription and OTC NSAIDs and a template for a medication guide to be distributed with the entire class of prescription products. The labeling changes resulting from this comprehensive analysis include additional warnings regarding the risks of SJS and TEN (discussion in section II.C of this response). For a comprehensive posting of FDA's actions regarding NSAIDs, see our Web site at www.fda.gov/cder/drug/infopage/COX2.

II. DISCUSSION

A. Review of Adverse Event Reporting System (AERS) Data

You have requested that FDA conduct a thorough assessment of the risks of developing SJS or TEN associated with the use of prescription and OTC ibuprofen drug products (Petition at 1). FDA uses a number of methods to monitor the safety of marketed drugs, including review of clinical trials submitted to FDA for marketing approvals, review of other clinical studies available in the scientific literature, and review of the Adverse Event Reporting System (AERS) surveillance database implemented in 1997. As you recognize in your petition (based on the thorough citation of the clinical studies from publicly available literature (Petition at 10-17)), clinical trials provide strong evidence of the potential for adverse reactions associated with a particular drug.

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[1] Fritsch, P.O., and A. Sidoroff, "Drug-Induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis," *American Journal of Clinical Dermatology,* 1(6):349-360, Nov-Dec 2000; Wolkenstein P., and J. Revuz, "Drug-Induced Severe Skin Reactions. Incidence, Management and Prevention," *Drug Safety*, 13(1):56-68, July 1995; and Mockenhaupt, M., et al., "The Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Associated with Nonsteroidal Anti-Inflammatory Drugs: A Multinational Perspective," *Journal of Rheumatology*, 30:2234-2240, 2003.

You state that the frequency of SJS has been estimated to be as high as 49 to 60 cases per million (Petition at 20, citing Strom et al., *Statistics in Medicine*, 1991). You also state that the incidence of SJS and TEN is approximately 6 or 7 cases per 100,000, citing the Boston University Fever Study (BUFS) and *Cecil Textbook of Medicine*, 19th edition (Petition at 20).[2]

We believe that the available evidence, including but not limited to adverse events reports, indicates that the incidence of SJS and TEN is less than the cited estimate of 6 or 7 cases per 100,000. Based on our review of the literature (including BUFS, Children's Analgesic Medicine Project and other, more recent study reviews, including those cited in the Petition at 10-17), we estimate the overall incidences of SJS and TEN range from 1.2 to 6 per million per year and 0.4 to 1.2 per million per year, respectively.[3]

BUFS, which was reviewed by FDA in 1995 during the prescription-to-OTC switch of ibuprofen suspension, was a randomized, active drug-controlled, double-blind, practitioner-based trial in 83,915 febrile children, ages 6 months to 12 years. The study was specifically designed to assess the safety of ibuprofen 5 milligrams (mg)/kilograms (kg) and ibuprofen 10 mg/kg relative to acetaminophen 12 mg/kg in the treatment of febrile children. A total of 55,785 patients received ibuprofen suspension (27, 948 received a 5 mg/kg dose and 27,837 received a 10 mg/kg dose) and 28,130 received acetaminophen 12 mg/kg. While there were no cases of SJS or TEN reported during the 4-week follow-up study, there were four cases of erythema multiforme reported (one in the acetaminophen group, one in the ibuprofen 5 mg/kg group, and two in the ibuprofen 10 mg/kg group).[4] The incidences of one per 28,130

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[2] Note that *Cecil Textbook of Medicine*, 22d Ed., 2004, does not include an incidence rate for SJS or TEN.

[3] See Wolkenstein, P., et al.; Mockenhaupt, M., et al., *supra* note 1; Chan, H.L, et al., "The Incidence of Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis. A Population-Based Study with Particular Reference to Reactions Caused by Drugs Among Outpatients," *Archives of Dermatology*, 126(1):43-47, 1990; Strom, B.L, et al., "A Population-Based Study of Stevens-Johnson Syndrome. Incidence and Antecedent Drug Exposures," *Archives of Dermatology*, 127(6):831-838, 1991; Rzany, B. et al., "Epidemiology of Erythema Exsudativum Multiforme Majus, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis in Germany (1990-1992): Structure and Results of a Population-Based Registry," *Journal of Clinical Epidemiology*, 49(7):796-773, 1996. It is worth noting that the oxicam NSAIDs are nearly always implicated with a higher risk than the propionic NSAIDs (which includes Ibuprofen). In one study, the multivariate relative risk for the group of propionic acid NSAIDs did not reach statistical significance. Roujeau, J.C., et al., "Medication Use and the Risk of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis," *New England Journal of Medicine*, 333(24):1600-7, 1995.

[4] Erythema multiforme is a skin reaction in the same family as SJS and TEN. Classification of these reactions in five categories is based on clinical criteria proposed by Roujeau:

- Bullous erythema multiforme, detachment below 10% of the body surface area (BSA) plus localized typical targets or raised atypical targets
- SJS, detachment below 10% of the BSA plus widespread erythematous or purpuric macules or flat atypical targets
- Overlap SJS/TEN, detachment between 10% and 30% of the BSA plus widespread purpuric macules or flat atypical targets
- TEN with spots, detachment above 30% of the BSA plus wide-spread purpuric macules or flat atypical targets

in the acetaminophen group, one per 27,948 in the 5 mg/kg ibuprofen group, and two per 27,837 in the 10 mg/kg ibuprofen group were extrapolated into 3.6, 3.6, and 7.2 per 100,000 respectively. On further review of these four cases, it is not clear whether they were caused by the study drugs, by other concomitantly used drugs (such as antibiotics), or by the disease for which the patient received drug treatment.

In addition, in response to your request, we reviewed the U.S. postmarketing adverse event reports of SJS and TEN in association with the use of ibuprofen products. Adverse event cases gathered in the AERS database come from different sources, including serious adverse events reported directly to the manufacturers of the drugs. AERS can be used to very effectively identify serious, unexpected rare events that were not detected during the drug's clinical trials, but the system also has well-known limitations. Challenges to using AERS include: (1) AERS reports are not systematically collected; (2) AERS reports are often missing important clinical information; (3) patients may have other drug exposures that make attribution difficult; and (4) reporters can be influenced by media or other external pressures.

We searched the AERS database for domestic reports of SJS and TEN associated with all ibuprofen products (prescription and OTC) during its marketing history from 1975 through March 2005. The AERS database search retrieved 88 cases, of which 49 were possibly related to the use of ibuprofen products: 31 cases reported SJS and 18 cases reported TEN. There was no noticeable trend over the years in reporting of adverse events given the small number of reports received per year. Of the 49 cases, 13 reported the use of an OTC ibuprofen product and 17 reported the use of a prescription ibuprofen product; the remaining cases did not specify this information. The age of patients ranged from 16 months to 81 years with the median age of 23 years. There were 21 pediatric cases (less than or equal to 17 years old). Thirty-one cases reported the concomitant use of other medications, of which 10 cases reported the concomitant use of a co-suspect drug that has been associated with SJS and/or the development of TEN. The median time to onset of the event was 3 days with a range from one dose to 10 weeks. The doses ranged from 200 mg to 3200mg/day. Serious outcomes included 5 deaths and 38 hospitalizations. Three cases of death, including one identified in your petition, may have been related to TEN and the use of ibuprofen. The causes of death in the other two cases were not specified, and again, these cases involved co-suspect drugs.

Putting these numbers in context, there are approximately 29 million prescriptions dispensed per year in the U.S. retail setting for prescription single-ingredient ibuprofen tablets, oral liquids, and suspensions, or combination products containing ibuprofen [5] and probably more than 100 million users of OTC ibuprofen per year.

- TEN without spots, detachment above 10% of the BSA with large epidermal sheets and without any purpuric macules or target

Roujeau, J.C., "The Spectrum of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Clinical Classification," *Journal of Investigative Dermatology*, 102(6):28S-30S, 1994.

[5] IMS Health, National Prescription Audit *Plus*™, Years 2002, 2003 and 2004, Data Extracted August 2005.

We recognize that there is a risk of SJS and TEN associated with the use of ibuprofen products. However, our analysis of AERS and other data indicates that the risk is not as great as you assert in the petition.

In your petition, you compare the incidence and frequency of SJS and TEN associated with the use of ibuprofen products with the incidence and frequency of Reye's syndrome associated with the use of aspirin and conclude that the benefit-risk balance is analogous (Petition at 19-21).

First, as discussed, we believe that the risks, in terms of incidence and frequency, of SJS and TEN associated with ibuprofen are significantly less than cited in the petition. The incidence of Reye's syndrome before 1982 (prior to the Reye's syndrome warning implementation for salicylate-containing drug products) was greater than is the incidence of SJS and TEN. Specifically, it was estimated that overall incidence of Reye's syndrome in persons under 18 years of age was 0.37 to 4.7 per 100,000, and in persons who contracted influenza B was 30 to 60 per 100,000.[6] This risk was significantly greater than the estimated 1.2 to 6 per million per year for SJS and the estimated 0.4 to 1.2 per million per year for TEN.

In addition, you claim that the mortality rate for SJS ranges from 5 to 30 percent and up to 80 percent for TEN (Petition at 20). Based on our review of the literature, SJS is fatal in approximately 5 percent of incidences and TEN is fatal in approximately 30 percent of incidences.[7] The mortality rate for Reye's syndrome reported to the Center for Disease Control (CDC) at the time of the Reye's syndrome warning implementation was between 20 and 30 percent.[8]

However, even if the frequency-rate and rate of fatality were comparable to that of Reye's syndrome and aspirin, we do not believe that Reye's syndrome offers an analogous benefit-risk balance. Although Reye's syndrome is a disease of unknown cause, we do know that it is precipitated by the use of aspirin during a viral illness, mainly chicken pox and influenza.[9] Therefore, Reye's syndrome is preventable, in the sense that we can warn people not to use aspirin if they may have a viral illness. SJS and TEN, on the other hand, are not associated with any particular risk factors and, therefore, are unpredictable. We can warn users to beware of the symptoms of SJS and TEN, but we do not know under what circumstances to avoid the use of ibuprofen or other NSAIDs altogether.

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[6] "Reye's Syndrome — Epidemiological Considerations," *Lancet*, 1(8278):941-943, 1982.

[7] Wolkenstein, P., et al.; Mockenhaupt, M., et al., *supra* note 1; and *Cecil Textbook of Medicines*, 22[d] Ed., 2004.

[8] CDC, "Follow-up on Reye Syndrome-United States," *Morbidity and Mortality Weekly Report*, 29:321-322, 1980; CDC, "National Surveillance for Reye Syndrome, 1981: Update, Reye Syndrome and Salicylate Usage," *Morbidity and Mortality Weekly Report*, 31(5):53-60, 1982.

[9] *Id.* and Sullivan-Bolyai et al., "Epidemiology of Reye Syndrome," *Epidemiologic Reviews*, 3:1-26, 1981.

B. Manufacturers' Conduct

You state that manufacturers of ibuprofen drug products have withheld safety information regarding the risks of SJS and TEN associated with ibuprofen products and request FDA to conduct an investigation accordingly. You state that "McNeil and Wyeth have failed to provide the FDA full information regarding the safety issues surrounding serious skin reactions, including SJS/TEN that were not presented in their applications for their OTC pediatric formulations" (Petition at 9). However, you provide no evidence to support this allegation. In addition, we have no evidence that there is additional undisclosed safety information that was withheld by ibuprofen manufacturers. If you have any information to support this allegation, please provide it to us.

Ibuprofen products, whether OTC or prescription, are marketed only under a new drug application (NDA) or abbreviated NDA (ANDA). Therefore, manufacturers of ibuprofen must comply with the safety reporting requirements for approved NDAs and ANDAs (21 CFR 314.80 and 314.81). Under these regulations, manufacturers must report all serious, adverse drug experiences whether the ibuprofen is marketed as prescription or OTC. In either case, if a manufacturer receives a report of SJS or TEN associated with the use of a prescription or OTC product, it would be considered a serious, expected adverse drug experience and must be reported. SJS and TEN are categorized as "expected" events because they are listed in the current labeling for the drug product. Therefore, manufacturers are required to submit reports they have received of SJS and TEN to FDA annually in periodic reports under § 314.80(c)(2). Again, we have no evidence that manufacturers are not complying with these reporting requirements. Therefore, we see no actionable allegation to pursue.

C. Communication of Risk Information

You request FDA to require additional warnings in the labeling of both prescription and OTC ibuprofen to warn prescribers and consumers about the risks of SJS and TEN associated with the use of ibuprofen. You request that FDA issue "Dear Doctor" and "Dear Healthcare Professional" letters to educate the healthcare community about these risks. In addition, you request that FDA obtain ibuprofen foreign labels, and that they be translated into English and disseminated to the public. Finally, with regard to OTC ibuprofen, you recommend that FDA reconsider the OTC status of the pediatric formulation of ibuprofen (Petition at 1-2, 19-24).

As discussed in section I of this response, in April 2005, FDA issued a press release that included a statement about potential skin reactions associated with the use of NSAIDs and announced that the Agency is asking manufacturers of OTC NSAIDs to include a warning about potential skin reactions. In addition, FDA posted a public health advisory, a "question and answer" education tool that includes a question on SJS and potentially life-threatening skin reactions, supplemental request letters, and labeling templates (www.fda.gov/cder/drug/infopage/COX2). We believe that this comprehensive effort responds to the actions that you have requested in your petition.

1. Prescription Ibuprofen

In your petition at 23, you recommend the Agency take the following actions regarding ibuprofen prescription drug labeling and risk communication:

- Add a bolded black box warning against erythema multiforme, SJS, and TEN, describing the associated symptoms, potential outcomes and recommended actions
- Issue Dear Doctor and Dear Healthcare Professional letters

We agree that revisions to labeling are necessary to make more explicit the risks associated with SJS and TEN. Therefore, your request for labeling revisions has been granted. We have requested that manufacturers change the labeling for all NSAIDs, including ibuprofen, to include a description of early symptoms associated with SJS and TEN in the **Skin Reactions** section in **WARNINGS**, as follows:

> **Skin Reactions**
> NSAIDs, including TRADENAME, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

In addition, we have requested that the **Information for Patients** section of **PRECAUTIONS** read as follows:

> TRADENAME, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

However, we do not believe that the risk-benefit balance warrants inclusion of a bolded black box warning. Therefore, this aspect of your request is denied.

As discussed in section I of this response, we conducted a thorough analysis of risks associated with all NSAIDs. As a result of that analysis, we concluded that the cardiovascular risks and the gastrointestinal risks rise to the level warranting a bolded black box warning for all NSAID products. For a template of the bolded black box warning for NSAIDs, see www.fda.gov/cder/drug/infopage/COX2/NSAIDRxTemplate.pdf. FDA compared the risks of SJS/TEN associated with the different types of NSAID products and concluded that there was a greater risk with certain of the COX-2 selective NSAID products than with the older, non-selective NSAID, ibuprofen products. (See section II.A of this document for a discussion of the

risks associated with ibuprofen products.) As a result, two of the COX-2 selective NSAID products (valdecoxib and rofecoxib) have been withdrawn from marketing. However, FDA concluded that for ibuprofen products, the labeling changes proposed are appropriate and that a boxed warning is not warranted at this time.

As part of this comprehensive risk-benefit analysis, FDA decided to require a NSAID Medication Guide under 21 CFR part 208 that accompanies each prescription dispensed (http://www.fda.gov/cder/drug/infopage/COX2/NSAIDmedguide.htm). One of the serious side effects listed within the Medication Guide is "life-threatening skin reactions." In addition, it directs patients to "Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms," which include "itching," "flu-like symptoms," and "skin rash or blisters with fever."

We believe that the public health advisory, press announcements, and educational tools that we have developed, within the context of a comprehensive prescriber and consumer awareness and education campaign, are the most effective mechanisms to alert the healthcare community and NSAID consumers about the serious risks associated with these products.

2. OTC Ibuprofen

You recommend that FDA reconsider the OTC status of the pediatric formulation of ibuprofen or, at a minimum, add the following changes to ibuprofen OTC labeling:

- In the "***Warnings***" of the labeling: "**Serious Skin Reactions:** Ibuprofen may cause serious skin reactions that begin as rashes and blisters on the skin, and in the areas of the eyes, mouth and genitalia. These early symptoms may progress to more serious and potentially life-threatening diseases, including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Seek immediate attention if any of these symptoms develop while taking ibuprofen."

- In the "***Stop use and ask a doctor if***": "a skin rash or blisters on the eyes, mouth or genitalia occur because these symptoms may be an early sign of rare and life-threatening reactions including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermonecrolysis."

(Petition at 23-25).

We agree that the labeling for OTC NSAIDs, including all ibuprofen products, should be improved to warn consumers about the risks of severe skin reactions associated with OTC ibuprofen products (see Decision Memo at 15-16). As a result, we have requested that manufacturers include under the ***Allergy alert*** subheading the symptoms associated specifically with SJS and TEN. We do not believe that it is useful to include the specific terms *SJS*, *TEN*, or *erythema multiforme*, *Stevens-Johnson syndrome*, and *toxic epidermal necrolysis* in the OTC label because most consumers are unfamiliar with these terms. In addition, effective OTC labeling communicates warning information in a manner that

consumers can quickly and easily identify and understand. Consequently, we believe a description of symptoms is more appropriate. Therefore, prominently displayed under the ***Allergy alert*** subheading in the Drug Facts Label, the labeling will include:

- skin reddening
- rash
- blisters

In addition, under the ***Allergy alert*** subheading, the labeling will state: "If an allergic reaction occurs, stop use and seek medical help right away." We believe that adding these symptoms to the ***Allergy alert***, with advice to stop use and seek medical attention immediately, will alert and educate consumers to the nature of the allergic reactions associated with SJS and TEN. Further, we intend to continue our consumer education efforts regarding the safe and effective use of OTC pain relievers.

We disagree, however, with your request that we reconsider the OTC status of the pediatric formulation of ibuprofen. As discussed above, we believe that the incidence of SJS or TEN is not as great as cited. We believe that the overall benefit versus risk profile for ibuprofen products remains very favorable when they are used according to the labeled instructions. It is in the interest of the public health to maintain in the pediatric OTC market a range of therapeutic options for the short-term relief of pain. Further, as discussed in greater detail in the Decision Memo (at 15), other available OTC drugs for short-term relief of pain and fever can also be associated with serious, potentially life-threatening adverse events in certain settings and patient populations.

Finally, you request FDA to obtain foreign labels, translate them into English, and disseminate them to the American public (Petition at 19). We received some foreign OTC ibuprofen product labeling and recognize that there is variation in the information provided internationally. However, as a result of our extensive, comprehensive revision of both OTC and prescription labeling for all NSAID products, we believe that the revised labeling templates for both OTC and prescription ibuprofen products most appropriately communicate the risks and benefits associated with their use. Enclosed are: (1) the labeling template for the new Drug Facts label for adult and pediatric OTC ibuprofen drug products; (2) the labeling template for ibuprofen prescription labeling; and (3) the Medication Guide that must accompany ibuprofen prescription drug products.

III. CONCLUSION

For the above stated reasons, your petition is granted in part and denied in part.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research

Enclosures

ADULT DRUG FACTS LABEL:

Drug Facts
Active ingredient (in each [insert dosage unit]) ***Purpose*** [*insert* active ingredient] XXX mg (NSAID)*.....Pain reliever/fever reducer * nonsteroidal anti-inflammatory drug
Uses • [add NDA approved uses]
Warnings **Allergy alert:** [*insert* active ingredient] may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include: • hives • facial swelling • asthma (wheezing) • shock • skin reddening • rash • blisters If an allergic reaction occurs, stop use and seek medical help right away. **Stomach bleeding warning:** This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you: • are age 60 or older • have had stomach ulcers or bleeding problems • take a blood thinning (anticoagulant) or steroid drug • take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others] • have 3 or more alcoholic drinks every day while using this product • take more or for a longer time than directed
Do not use • if you have ever had an allergic reaction to any other pain reliever/fever reducer • right before or after heart surgery
Ask a doctor before use if you have • problems or serious side effects from taking pain relievers or fever reducers • stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain • ulcers • bleeding problems • high blood pressure • heart or kidney disease • taken a diuretic • reached age 60 or older
Ask a doctor or pharmacist before use if you are • taking any other drug containing an NSAID (prescription or nonprescription) • taking a blood thinning (anticoagulant) or steroid drug • under a doctor's care for any serious condition • taking any other drug

When using this product • take with food or milk if stomach upset occurs • long term continuous use may increase the risk of heart attack or stroke
Stop use and ask a doctor if • you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. • pain gets worse or lasts more than 10 days • fever gets worse or lasts more than 3 days • stomach pain or upset gets worse or lasts • redness or swelling is present in the painful area • any new symptoms appear
If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use [*NSAID active ingredient*] during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.
Directions • **do not take more than directed** • **the smallest effective dose should be used** • do not take longer than 10 days, unless directed by a doctor (see Warnings) • **[add NDA approved direction]**
Other information • [storage conditions]
Inactive ingredients [list ingredients in alphabetical order]
Questions or comments? call **1-800-XXX-XXXX:** [insert appropriate times when the phone will be answered by a person, e.g., weekdays 8AM to 11 PM EST; weekends 9AM to 11 PM, EST]

PEDIATRIC DRUG FACTS LABEL
(For Products Labeled Only for Children Under 12 Years of Age)

Drug Facts

Active ingredient (in each [insert dosage unit]) ***Purpose***

Ibuprofen XXX mg (NSAID)*.....Pain reliever/fever reducer

* nonsteroidal anti-inflammatory drug

Uses

- [add NDA approved uses]

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if the child:

- has had stomach ulcers or bleeding problems
- takes a blood thinning (anticoagulant) or steroid drug
- takes other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- takes more or for a longer time than directed

Sore throat warning: Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult doctor promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by doctor. [*For products with an approved "sore throat" indication*]

Do not use

- if the child has ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if the child has

- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- not been drinking fluids
- lost a lot of fluid due to vomiting or diarrhea
- high blood pressure
- heart or kidney disease
- taken a diuretic

Ask a doctor or pharmacist before use if the child is • taking any other drug containing an NSAID (prescription or nonprescription) • taking a blood thinning (anticoagulant) or steroid drug • under a doctor's care for any serious condition • taking any other drug
When using this product • take with food or milk if stomach upset occurs • long term continuous use may increase the risk of heart attack or stroke
Stop use and ask a doctor if • the child feels faint, vomits blood, or has bloody or black stools. These are signs of stomach bleeding. • stomach pain or upset gets worse or lasts • the child does not get any relief within first day (24 hours) of treatment • fever or pain gets worse or lasts more than 3 days • redness or swelling is present in the painful area • any new symptoms appear
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions • **this product does not contain directions or complete warnings for adult use** • **do not give more than directed** • do not give longer than 10 days, unless directed by a doctor (see Warnings) • [add NDA approved directions]
Other information • [storage conditions]
Inactive ingredients [list ingredients in alphabetical order]
Questions or comments? call **1-800-XXX-XXXX:** [insert appropriate times when the phone will be answered by a person, e.g., weekdays 8AM to 11 PM EST; weekends 9AM to 11 PM, EST]

PRINCIPAL DISPLAY PANEL:

Proprietary Name (if used) Established name (NSAID), XXX mg Pain reliever/fever reducer

OR

Proprietary Name (if used) Established name XXX mg Pain reliever/fever reducer (NSAID)

Proposed NSAID Package Insert Labeling Template1 (Revised XXX/05)

TRADENAME (Established name which should always include dosage form) Strength

Cardiovascular Risk

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

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

Gastrointestinal Risk

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

DESCRIPTION- No change

CLINICAL PHARMACOLOGY- No change

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of TRADENAME and other treatment options before deciding to use TRADENAME. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

TRADENAME is indicated:

* For reduction of fever [in patients age]
* For relief of mild to moderate pain [in patients age]
* For relief of signs and symptoms of juvenile arthritis.
* For relief of the signs and symptoms of rheumatoid arthritis
* For relief of the signs and symptoms of osteoarthritis.
* For treatment of primary dysmenorrhea.
* For acute or long-term use in the relief of signs and symptoms of the following:
    1. Ankylosing spondylitis
    2. Acute painful shoulder (Acute subacromial bursitis/supraspinatus tendinitis)
    3. Acute gouty arthritis

Put in the product specific indication(s)

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1 Throughout this package insert, the term NSAID refers to a non-aspirin non-steroidal anti-inflammatory drug.

CONTRAINDICATIONS

TRADENAME is contraindicated in patients with known hypersensitivity to GENERIC NAME.

TRADENAME should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS - Anaphylactoid Reactions**, and **PRECAUTIONS - Preexisting Asthma**).

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

WARNINGS

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events

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

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

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

Hypertension

NSAIDs, including TRADENAME, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including TRADENAME, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. TRADENAME should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects- Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including TRADENAME, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning

symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of TRADENAME in patients with advanced renal disease. Therefore, treatment with TRADENAME is not recommended in these patients with advanced renal disease. If TRADENAME therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to TRADENAME. TRADENAME should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS - Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including TRADENAME, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy
In late pregnancy, as with other NSAIDs, TRADENAME should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General
TRADENAME cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
The pharmacological activity of TRADENAME in reducing [fever and] inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.
Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including TRADENAME. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.
A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with TRADENAME. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), TRADENAME should be discontinued.
Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including TRADENAME. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including TRADENAME, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.
NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving TRADENAME who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.
Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, TRADENAME should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.
Information for Patients
Patients should be informed of the following information before initiating therapy with an

NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. TRADENAME, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Cardiovascular Effects**).

2. TRADENAME, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation**).

3. TRADENAME, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS**).

7. In late pregnancy, as with other NSAIDs, TRADENAME should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash,

etc.) or if abnormal liver tests persist or worsen, TRADENAME should be discontinued.

Drug Interactions

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin

[When TRADENAME in administered with aspirin, its protein binding is reduced, although the clearance of free TRADENAME is not altered. The clinical significance of this interaction is not known; however,] as with other NSAIDs, concomitant administration of GENERIC NAME and aspirin is not generally recommended because of the potential of increased adverse effects.

Furosemide

Clinical studies, as well as post marketing observations, have shown that TRADENAME can reduce the natriuretic effect-of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **PRECAUTIONS, Renal Effects**), as well as to assure diuretic efficacy.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Drug/Laboratory Test Interactions

Only if positive interactions have been observed. (See 201.57 (f)(4)(N).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Usually only if significant findings have been observed. (See 201.57 (f)(5))

Pregnancy

Teratogenic Effects. Pregnancy Category C.

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of

TRADENAME on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human-milk and because of the potential for serious adverse reactions in nursing infants from TRADENAME, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of ??? [have, have not] been established.

Geriatric Use

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS- No change

OVERDOSAGE- No change

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of TRADENAME and other treatment options before deciding to use TRADENAME. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

After observing the response to initial therapy with TRADENAME, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of ????, the recommended dose is ??? mg given orally ?? times per day.

[Different dose strengths and formulations (i.e., capsules, tablets, suspensions) of the drug are not necessarily bioequivalent. This difference should be taken into consideration when changing {formulation (type, strength)}.]

HOW SUPPLIED- No change

Medication Guide
for
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are use to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.

- Some of these NSAID medicines are sold in lower doses without a prescription (over –the –counter). Talk to your healthcare provider before using over –the –counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbirofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen

Generic Name	Tradename
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

This Medication Guide has been approved by the U.S. Food and Drug Administration.