DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA

SUPPLEMENTAL LABELING REQUEST - CBE

Company
Attention:

Dear,

Please refer to your new drug application(s) (NDA) approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act DRUG NAME, STRENGTH, FORM FOR (EACH NDA NUMBER).

We additionally refer to the February 16-18, 2005 joint meeting of the Arthritis and Drug Safety and Risk Management Advisory Committees to discuss the overall benefit to risk considerations (including cardiovascular (CV) and gastrointestinal (GI) safety concerns) of COX-2 selective and non-selective, non-steroidal anti-inflammatory drugs (NSAIDs) and related agents.

We also refer to FDA's letter dated April 7, 2005, requesting cardiovascular information regarding your drug.

Consistent with recommendations made by the committee members, and following a thorough review of all available data, we believe that labeling changes are warranted to include more specific information for consumers, family members, and caregivers about potential risks of CV and GI adverse effects associated with the use of non-prescription NSAIDs (excluding aspirin). For additional information, please see www.fda.gov/cder/drug/infopage/cox2/default.htm. On this page you can find links to a number of relevant documents including the decision memo entitled "Analysis and Recommendations for Agency Action - COX-2 Selective and Non-selective NSAIDS."

Therefore, we request that you revise the labeling for all of your over-the-counter (OTC) products that contain any of the following ingredients: ibuprofen, ketoprofen, or naproxen. We request that you revise your labeling as specified in the enclosed templates and that the revisions be made for all OTC adult and pediatric drug products that contain these ingredients. We include adult warnings on the pediatric products in this request because such products are sometimes used by adults who cannot take solid oral dosage forms. For that reason, on our own initiative, we are also granting an exemption under 21 C.F.R. § 201.66 (e) to replace the word "you" with the word "user" in the standard headings in 21 C.F.R. § 201.66 (c)(5)(iv) and (v) so that the revised headings read "Ask a doctor before use if the user has" and "Ask a doctor or pharmacist before use if the user is" to accommodate the warning language specified in the template for children. We intend to propose to codify this change to 21 C.F.R § 201.66 (c) in a future amendment to the rulemaking, at which time you will have an opportunity to comment on this language.

In addition, we request that you revise the "Allergy alert" and "Alcohol warning" for all of your OTC products that contain ibuprofen, ketoprofen or naproxen as specified in the enclosed templates. The "Allergy alert" for these products should be revised to include a warning for aspirin sensitive individuals and a description of early symptoms associated with Stevens-Johnson Syndrome (SJS). The "Alcohol warning" currently required by 21 C.F.R. § 201.322 should also be relocated to appear as part of the new stomach bleeding warning.

In addition to the revision of the Drug Facts label, we also request that the Principal Display Panel (PDP) for all of the above-described products display the word "NSAID" in parentheses following the name of the NSAID ingredient. The word "(NSAID)" should appear highlighted in either fluorescent or color contrast or in bold type. The size should be at least one-half as large as the size of the most prominent printed matter on the PDP. For 12 months after introduction into the OTC marketplace, please also add to the PDP the statement "See new warnings information". This statement should also be highlighted in either fluorescent or color contrast or in bold type and the size should be at least one-third the size of the most prominent printed matter on the PDP.

Attached are templates that we request you to follow in preparing new labeling:

1. Template Drug Facts label for all adult products
2. Template Drug Facts label for pediatric ibuprofen-containing products
3. Template for the Principal Display Panel

In addition to the above recommended language, the Drug Facts label must incorporate all previous revisions that were agreed upon in your most recently approved labeling. Also, notwithstanding the specific format changes we request above with respect to 21 C.F.R. § 201.66 (c)(iv) and (v), your labeling must otherwise be formatted in accordance with the requirements of 21 C.F.R. § 201.66.

We remind you that if you have a package insert, it should also be changed to reflect the above revisions.

These labeling revisions should be submitted to FDA in the form of a "Supplement – Changes Being Effected" within 30 days from the date of this letter in accordance with the requirements of 21 C.F.R. § 314.70. Color-mock up labeling can be submitted in lieu of final printed labeling. If you deviate from the attached templates you must submit a prior approval supplement for our review and comment.

The labeling changes should be implemented within 6 months. If you are unable to meet this deadline, contact us to discuss the timing of your new labeling.

If you have any questions, call Laura Shay, Regulatory Project Manager, at 301-827-2274.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Attachments:

1. Template Drug Facts label for all adult products
2. Template Drug Facts label for pediatric ibuprofen-containing product
3. Template for the Principal Display Panel

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
- with any other drug containing an NSAID (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure.

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

- under a doctor's care for any serious condition
- taking a blood thinning (anticoagulant) or steroid drug
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs
- taking longer than 10 days or more than the recommended dose 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:

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 user:

- 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
- has 3 or more alcoholic drinks every day while using this product
- is age 60 or older

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

Do not use

- if the user has ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery
- with any other drug containing an NSAID (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure.

Ask a doctor before use if the user 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
- reached age 60 or older

Ask a doctor or pharmacist before use if the user is ● under a doctor's care for any serious condition ● taking a blood thinning (anticoagulant) or steroid drug ● taking any other drug
When using this product ● take with food or milk if stomach upset occurs ● taking longer than 10 days or more than the recommended dose may increase the risk of heart attack or stroke
Stop use and ask a doctor if ● the user 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 user 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
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 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