DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

SUPPLEMENTAL LABELING REQUEST - CBE

NDA

Dear

Please refer to your New Drug Application approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug products containing a non-steroidal anti-inflammatory drug (NSAID):

We additionally refer to the September 19 and 20, 2002 Nonprescription Drugs Advisory Committee (NDAC) meeting discussing the potential for gastrointestinal (GI) bleeding and renal toxicity related to the use of over-the-counter (OTC) NSAIDs. We also refer to the February 16-18, 2005 joint meeting of the Arthritis and Drug Safety and Risk Management Advisory Committees discussing the overall benefit to risk considerations (including cardiovascular (CV) safety concerns) of COX-2 selective and non-selective NSAIDs and related agents.

We also refer to our letters dated April 7, 2005, and June 14, 2005.

We are providing updated templates for the labeling of non-prescription NSAIDs that contain any of the following ingredients: ibuprofen, ketoprofen, or naproxen. These templates supersede those enclosed in our letter of June 14, 2005. 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.

The following changes have been made to the templates for the Drug Facts label and Principal Display Panel (PDP) that we proposed in our letter on June 14, 2005:.

1. Pediatric Drug Facts template for products that are labeled only for children under 12 years of age:

    A. The following bolded statement should be added under the ***Directions*** heading: **"This product does not contain directions or complete warnings for adult use"**.

    B. The following warnings have been deleted:

        a. Under the heading ***Warnings***, **Stomach bleeding warning:**
            - is age 60 or older
            - has 3 or more alcoholic drinks every day while using this product

        b. Under the subheading **Ask a doctor before use if the user has:**
            - reached age 60 or older

c. The pregnancy/breast-feeding warning

C. The word "User" in the standard headings has been removed and replaced with the word "child" in accordance with 21 C.F.R. § 201.66 (c)(5)(iv) and (v).

Other warnings regarding concomitant use with other drugs (i.e. steroids, anti-coagulants, and diuretics) and conditions such as hypertension, heart and kidney disease are not unique to adults and are therefore required on all the products, whether they are intended exclusively for pediatric use or not.

2. Adult and Pediatric Drug Facts templates:

A. Under the subheading **Do not use,** due to the possible concomitant use of low dose aspirin, the statement "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." has been revised and relocated under the subheading **Ask a doctor or pharmacist before use**.

B. Under the subheading **When using this product,** the statement "taking longer than 10 days or more than the recommended dose may increase the risk of heart attack or stroke" has been replaced with the statement "long term continuous use may increase the risk of heart attack or stroke".

3. On the PDP, the word "NSAID" should be displayed in parentheses. The word "NSAID" should follow the name of the NSAID ingredient or follow the terms that describe its general pharmacological category(ies) or principal intended action(s) in a font size that is equal to or larger than that in the currently approved labeling for these statements.

Attached are revised templates that we request you to follow in preparing new labeling. They combine the revisions we requested in our letter of June 14, 2005 with the updates described above:

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

We remind you that in addition to the above changes, the Drug Facts label must incorporate all previous revisions that were agreed upon in your most recently approved labeling. Your labeling must also be formatted in accordance with the requirements of 21 C.F.R. § 201.66.
We also 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 approval prior to implementation.

The labeling changes should be implemented within 6 months. If you are unable to meet 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}

Charles Ganley, M.D.
Director
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

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)