Drugs

Public Health Advisory - FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

4/7/2005

Today, the Food and Drug Administration (FDA) is announcing that it has asked Pfizer, Inc. to voluntarily withdraw Bextra (valdecoxib) from the market. Pfizer has agreed to suspend sales and marketing of Bextra in the U.S., pending further discussions with the agency. FDA is also asking manufacturers of all marketed prescription NSAIDs, including Celebrex (celecoxib), a COX-2 selective NSAID, to revise the labeling (package insert) for their products to include a boxed warning and a Medication Guide. The boxed warning will highlight the potential for increased risk of cardiovascular (CV) events with these drugs and the well-described, serious, and potentially life-threatening gastrointestinal (GI) bleeding associated with their use. The Medication Guide will accompany every prescription NSAID at the time it is dispensed to better inform patients about the CV and GI risks. Finally, FDA is asking manufacturers of non-prescription (OTC) NSAIDs to revise their labeling to include more specific information about the potential GI and CV risks, and information to assist consumers in the safe use of the drug. This announcement does not apply to aspirin as it has clearly been shown to reduce the risk of serious adverse CV events in certain patient populations.

In reaching these decisions, FDA has carefully considered the available data on all of the NSAIDs. The Agency has also considered presentations, discussions, and votes from the joint public meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on February 16, 17, and 18, 2005 to discuss the CV safety concerns for these drugs along with their overall risk-benefit.

Specifically, FDA is requesting the actions listed below and will work closely with the manufacturers to ensure their timely implementation.

BEXTRA (valdecoxib tablets)

FDA has concluded that the overall risk versus benefit profile is unfavorable and has requested that Pfizer, the manufacturer of Bextra, **voluntarily withdraw Bextra** from the market. This request is based on:

- The lack of adequate data on the cardiovascular safety of long-term use of Bextra, along with the increased risk of adverse CV events in short-term coronary artery bypass surgery (CABG) trials that FDA believes may be relevant to chronic use.
- Reports of serious and potentially life-threatening skin reactions, including deaths, in patients using Bextra. The risk of these reactions in individual patients is unpredictable, occurring in patients with and without a prior history of sulfa allergy, and after both short- and long-term use.
- Lack of any demonstrated advantages for Bextra compared with other NSAIDs.

Pfizer has agreed to suspend sales and marketing of Bextra in the U.S., pending further discussions with the agency.

Patients currently taking Bextra should contact their physicians to consider alternative treatments.

CELEBREX (celecoxib tablets)

FDA has concluded that the benefits of Celebrex outweigh the potential risks in properly selected and informed patients. Accordingly, FDA will allow Celebrex to remain on the market and has asked Pfizer to take the actions listed below.

- Revise the Celebrex label to:
- Include a **boxed warning** containing the class NSAID warnings and contraindication (see below) about CV and GI risk, plus specific information on the controlled clinical trial data that demonstrate an increased risk of adverse CV events for celecoxib.
- Encourage prescribers to discuss with patients the potential benefits and risks of Celebrex and other treatment options before a decision is made to use Celebrex.

- Encourage practitioners to use the **lowest effective dose** for the shortest duration consistent with individual patient treatment goals.
- Include a **Medication Guide** as part of the labeling. It will be required to be given at the time the drug is dispensed to inform patients of the potential for CV and GI risk associated with NSAIDS, in general, and Celebrex specifically. The Medication Guide will inform patients of the need to discuss with their doctor the risks and benefits of using NSAIDs and the importance of using the lowest effective dose for the shortest duration possible.
- Commit to conduct a l**ong-term study** to address the safety of Celebrex compared to naproxen and other appropriate drugs. FDA will work with Pfizer to design this long-term study and ensure its timely initiation and completion.

Patients who are taking CELEBREX should discuss questions or concerns about this new information with their physician.

Non-Selective NSAIDs

A number of non-selective NSAIDs (prescription and non-prescription (over-the-counter (OTC)) are approved for marketing in the United States. A list of these products is attached and is also available at COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)[1].

Long-term controlled clinical trials have not been conducted with most of these NSAIDs. However, the available data suggest that use of these drugs may increase CV risk. It is very difficult to draw conclusions about the relative CV risk among the COX-2 selective and non-selective NSAIDs with the data available.

All sponsors of non-selective NSAIDs will be asked to conduct and submit to FDA a comprehensive review and analysis of available controlled clinical trial databases pertaining to their NSAID product(s) to which they have access to further evaluate the potential for increased CV risk.

FDA will work closely with sponsors and other interested stakeholders (e.g., NIH) to encourage additional long-term controlled clinical trials of non-selective NSAIDs to further evaluate the potential for increased CV risk.

In addition, FDA is requesting labeling changes for both prescription and OTC non-selective NSAIDs. Because the use and labeling for the prescription products is different from those available without a prescription, they are addressed separately.

Prescription Non-Selective NSAIDs

FDA will request that manufacturers of all prescription products containing non-selective NSAIDs revise their product labeling to include:

- A boxed warning regarding the potential serious adverse CV events and the serious, and potentially life-threatening GI adverse events associated with the use of this class of drugs.
- A contraindication for use in patients who have recently undergone coronary artery bypass surgery.
- A Medication Guide for patients regarding the potential for CV and GI adverse events associated with the use of this class of drugs. The Medication Guide will be required to be given to patients at the time each prescription is dispensed. The Medication Guide will also inform patients of the need to discuss with their doctor the risks and benefits of using NSAIDs and the importance of using the lowest effective dose for the shortest duration possible if treatment with an NSAID is warranted for an individual patient.

Patients who are taking a prescription non-selective NSAID should discuss questions or concerns about this new information with their physician.

OTC Non-Selective NSAIDs

The available data do not suggest an increased risk of serious CV events for the short-term, low-dose use of the NSAIDs available over the counter. FDA will allow these products to remain on the market, but will request changes to the label to better inform consumers regarding the safe use of these products.

FDA will ask manufacturers of all OTC products containing ibuprofen (Motrin, Advil, Ibu-Tab 200, Medipren, Cap-Profen, Tab-Profen, Profen, Ibuprohm), naproxen (Aleve), and ketoprofen (Orudis, Actron) to revise their labeling to include:

- More specific information about the potential CV and GI risks,
- Instructions about which patients should seek the advice of a physician before using these drugs,
- Stronger reminders about limiting the dose and duration of treatment in accordance with package instructions,

unless otherwise advised by a physician, and

- A warning about potential skin reactions.

Patients who are taking an OTC NSAID should carefully follow the labeled directions, particularly with regard to dose and duration of use, and should contact their physician regarding any questions or concerns they may have about this new information.

Note: Aspirin is a nonselective NSAID. However, aspirin is also a platelet inhibitor and has been shown in clinical trials to reduce the risk of CV events. Patients taking aspirin to prevent CV events should NOT stop taking it, unless specifically advised to do so by their physician.

FDA expects that these actions will further encourage the safe and effective use of these products. FDA will continue to notify health care providers and patients in a timely fashion as new information becomes available.

FDA urges health care providers and patients to report adverse event information to the MedWatch program, using the contact information at the bottom of this page.

COX-2 Selective Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Prescription and Over-the-Counter (OTC) Non-selective NSAIDs Approved Under New Drug Application (NDA) Abbreviated New Drug Application (ANDA)

COX-2 Selective NSAIDs

Chemical Name	Brand Name
Celecoxib	Celebrex
Valdecoxib	Bextra
Rofecoxib	Vioxx

Non-selective NSAIDs

Chemical Name	Brand Name
Diclofenac	Cataflam, Voltaren, Arthrotec (combination with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen**	Motrin, Motrin IB, Motrin Migraine Pain, Advil, Advil Migraine Liqui-gels, Ibu-Tab 200, Medipren, Cap-Profen, Tab-Profen, Profen, Ibuprohm, Children's Elixsure *, Vicoprofen (combination with hydrocodone), Combunox (combination with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen**	Oruvail, Orudis, Actron
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen**	Aleve, Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

*There are many OTC Combinations with ibuprofen: Advil Cold And Sinus, Advil Cold, Advil Allergy Sinus, Children's Advil Allergy Sinus, Ibuprohm Cold and Sinus, Sine-Aid IB, Children's Motrin Cold.

**There are over-the-counter versions of these prescription medications.

Related Information

- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)[2]

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MedWatch Online[3]

Regular Mail: Use postage-paid FDA Form 3500[4]

Mail to: MedWatch 5600 Fishers Lane
Rockville, MD 20857

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