

FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes

Safety Announcement

[7-9-2015] The U.S. Food and Drug Administration (FDA) is strengthening an existing label warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the chance of a heart attack or stroke. Based on our comprehensive review of new safety information, we are requiring updates to the drug labels of all prescription NSAIDs. As is the case with current prescription NSAID labels, the Drug Facts labels of over-the-counter (OTC) non-aspirin NSAIDs already contain information on heart attack and stroke risk. We will also request updates to the OTC non-aspirin NSAID Drug Facts labels.

Patients taking NSAIDs should seek medical attention immediately if they experience symptoms such as chest pain, shortness of breath or trouble breathing, weakness in one part or side of their body, or slurred speech.

NSAIDs are widely used to treat pain and fever from many different long- and short-term medical conditions such as arthritis, menstrual cramps, headaches, colds, and the flu. NSAIDs are available by prescription and OTC. Examples of NSAIDs include ibuprofen, naproxen, diclofenac, and celecoxib (see Table 1 for a list of NSAIDs).

The risk of heart attack and stroke with NSAIDs, either of which can lead to death, was first described in 2005 in the *Boxed Warning* and *Warnings and Precautions* sections of the prescription drug labels. Since then, we have reviewed a variety of new safety information on prescription and OTC NSAIDs, including observational studies,¹ a large combined analysis of clinical trials,² and other scientific publications.¹ These studies were also discussed at a joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee held on [February 10-11, 2014](#).

Based on our review and the advisory committees' recommendations, the prescription NSAID labels will be revised to reflect the following information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for

all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.

- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

We will request similar updates to the existing heart attack and stroke risk information in the Drug Facts labels of OTC non-aspirin NSAIDs.

In addition, the format and language contained throughout the labels of prescription NSAIDs will be updated to reflect the newest information available about the NSAID class.

Patients and health care professionals should remain alert for heart-related side effects the entire time that NSAIDs are being taken. We urge you to report side effects involving NSAIDs to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Facts about non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs)

- NSAIDs are a class of medicines available by prescription and over-the-counter (OTC). They are some of the most commonly used pain medicines.
- NSAIDs are used to treat pain and fever from medical conditions such as arthritis, menstrual cramps, headaches, colds, and the flu.
- Examples of NSAIDs include ibuprofen, naproxen, diclofenac, and celecoxib. See Table 1 for a list of non-aspirin NSAIDs.

Additional Information for Patients and Consumers

- Non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the chance of a heart attack or stroke, either of which can lead to death. There are a large number of studies that support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied. These serious side effects can occur as early as the first weeks of using an NSAID and the risk may increase the longer you are taking an NSAID.

- The risk appears greater at higher doses; use the lowest effective amount for the shortest possible time.
- Seek medical attention immediately if you experience symptoms such as:
 - Chest pain
 - Shortness of breath or trouble breathing
 - Sudden weakness or numbness in one part or side of the body
 - Sudden slurred speech
- Many medicines contain NSAIDs, including those used for colds, flu, and sleep, so it is important to read the labels and avoid taking multiple medicines that contain NSAIDs.
- Patients who take low-dose aspirin for protection against heart attack and stroke should know that some NSAIDs, including those in over-the-counter (OTC) products such as ibuprofen and naproxen, can interfere with that protective effect.
- Read the patient Medication Guide you receive with your NSAID prescription. It explains the risks associated with the use of the medicine. You may access Medication Guides by clicking on this [link](#).
- Read the Drug Facts label before taking an OTC NSAID. Talk to your health care professional or pharmacist if you have questions or concerns about NSAIDs or which medicines contain them.
- Report side effects from NSAIDs to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, either of which can be fatal. There are a large number of studies that support this finding, with varying estimates of how much the risk is increased. Estimates of increased risk range from 10 percent to 50 percent or more, depending on the drugs and the doses studied. This risk may occur as early as the first weeks of treatment and may increase with duration of use.
- Remain alert for the development of cardiovascular adverse events throughout the patient's entire treatment course, even in the absence of previous cardiovascular symptoms.
- Inform patients to seek medical attention immediately if they experience symptoms of heart attack or stroke such as chest pain, shortness of breath or trouble breathing, sudden weakness or numbness in one part or side of the body, or sudden slurred speech.
- Encourage patients to read the Medication Guide for prescription NSAIDs and the Drug Facts label for over-the-counter (OTC) NSAIDs.
- Based on available data, it is unclear whether the risk for cardiovascular thrombotic events is similar for all non-aspirin NSAIDs.
- The increase in cardiovascular thrombotic risk has been observed most consistently at higher doses.
- The relative increase in serious cardiovascular thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known

cardiovascular disease or risk factors for cardiovascular disease. However, patients with known cardiovascular disease or risk factors had a higher absolute incidence of serious cardiovascular thrombotic events due to their increased baseline rate.

- To minimize the risk for an adverse cardiovascular event in patients treated with an NSAID, prescribe the lowest effective dose for the shortest duration possible.
- Some NSAIDs, including those in OTC products such as ibuprofen and naproxen, can interfere with the antiplatelet action of low dose aspirin used for cardioprotection by blocking aspirin's irreversible COX-1 inhibition.
- Report adverse events involving NSAIDs to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

FDA reviewed a meta-analysis of randomized clinical trials of cardiovascular and upper gastrointestinal events with non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), conducted by the Coxib and traditional NSAID Trialists' (CNT) Collaboration of the Clinical Trial Service and Epidemiological Studies Units at Oxford University.² We also reviewed observational studies and other scientific publications in the medical literature.¹ The findings of these studies were discussed at a joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee held on February 10-11, 2014 (for complete safety reviews, background information, and minutes of this meeting, click [here](#)).

Based on our comprehensive review and the recommendations from the advisory committees, we are requiring label changes to reflect the following conclusions:

- A large number of studies support the finding that NSAIDs cause an increased risk of serious cardiovascular thrombotic events, with varying estimates of how much the risk is increased. Estimates of increased relative risk range from 10 percent to 50 percent or more, depending on the drugs and the doses studied.
- Several observational studies found a significant cardiovascular risk within days to weeks of NSAID initiation. Some data also showed a higher risk with longer NSAID treatment.
- There are observational data indicating that the thrombotic cardiovascular risk from NSAID use is dose-related. There is also some evidence of this dose-response effect from clinical trials of celecoxib.
- Some observational studies and the CNT meta-analysis suggested that naproxen may have a lower risk for cardiovascular thrombotic events compared to the other NSAIDs; however, the observational studies and the indirect comparisons used in the meta-analysis to assess the risk of the nonselective NSAIDs have limitations that affect their interpretability. The variability in patients' risk factors, comorbidities, concomitant medications and drug interactions, doses being used, duration of treatment, etc., also need to be taken into consideration to make valid

comparisons. Importantly, these studies were not designed to demonstrate superior safety of one NSAID compared to another.

- There is evidence of an increased cardiovascular risk from NSAID use by apparently healthy patients. Data from the CNT meta-analysis, individual randomized controlled trials, and observational studies showed that the relative increase in cardiovascular thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known cardiovascular disease or risk factors for cardiovascular disease. However, patients with known cardiovascular disease or risk factors had a higher absolute incidence of excess cardiovascular thrombotic events due to their increased baseline rate.
- The CNT meta-analysis demonstrated an approximately two-fold increase in hospitalizations for heart failure with use of both COX-2 selective and nonselective NSAIDs. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of myocardial infarction, hospitalization for heart failure, and death.

The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial, is a large, ongoing randomized safety trial comparing cardiovascular event rates among patients with high cardiovascular risk who are randomized to celecoxib, naproxen, or ibuprofen. This trial was also discussed at the February 2014 Advisory Committee meeting and is expected to provide additional safety information.

Table 1. List of non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs)

| Generic name | Brand name(s) |
|---------------------|---|
| celecoxib | Celebrex |
| diclofenac | Cambia, Cataflam, Dyloject, Flector, Pennsaid, Solaraze, Voltaren, Voltaren-XR, Zipsor, Zorvolex, Arthrotec (combination with misoprostol) |
| diflunisal | No brand name currently marketed |
| etodolac | No brand name currently marketed |
| fenoprofen | Nalfon |
| flurbiprofen | Ansaid |
| ibuprofen* | Advil, Caldolor, Children's Advil, Children's Elixsure IB, Children's Motrin, Ibu-Tab, Ibuprohm, Motrin IB, Motrin Migraine Pain, Profen, Tab-Profen, Duexis (combination with famotidine), Reprexain (combination with hydrocodone), Vicoprofen (combination with hydrocodone) |
| indomethacin | Indocin, Tivorbex |
| ketoprofen | No brand name currently marketed |
| ketorolac | Sprix |
| mefenamic acid | Ponstel |
| meloxicam | Mobic |
| nabumetone | No brand name currently marketed |
| naproxen* | Aleve, Anaprox, Anaprox DS, EC-Naprosyn, Naprelan, Naprosyn, Treximet (combination with sumatriptan), Vimovo (combination with esomeprazole) |
| oxaprozin | Daypro |
| piroxicam | Feldene |
| sulindac | Clinoril |
| tolmetin | No brand name currently marketed |

*There are many over-the-counter (OTC) products that contain this medicine.

References

1. Food and Drug Administration [Internet]. Silver Spring, MD. FDA Briefing Information for the February 10-11, 2014 Joint Meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee. Available from:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM383180.pdf>. Accessed December 23, 2014.

2. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:769-79.