

Points for Discussion

Nonprescription Drugs Advisory Committee

September 20, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Hilton, Silver Spring Maryland

Issue: Aspirin and Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Gastrointestinal and Renal Toxicity

The Agency is in the process of writing a final regulation for internal analgesic drug products in the OTC drug review. This process began in 1977 with publication of the panel report and continued in 1988 with publication of the tentative final monograph. As part of the continuing review of this monograph, it is important to look at recent data pertinent to several safety issues that have been discussed in previous federal register notices.

Background

The Agency believes that aspirin, non-aspirin salicylates and NSAIDs are safe and effective OTC products that benefit tens of millions of consumers every year when used as directed. The Agency believes that these products should continue to be available OTC. Aspirin, non-aspirin salicylates and NSAIDs have long been very effective OTC drug products for the intermittent treatment of minor aches and pains. Aspirin, has the added benefit of reducing the risk of serious cardiovascular events when taken on a daily basis under the direction of a physician and is also effective in treating a variety of rheumatologic diseases. At their recommended OTC doses, these products are only rarely associated with serious adverse events.

Aspirin as an OTC product is somewhat unique in that it has professional labeling for the cardiovascular and rheumatologic indications. The professional labeling is similar in structure to a prescription label by providing information on the studies supporting efficacy, the indications, dosage recommendations, and warnings. The professional labeling for aspirin discusses the potential risk of gastrointestinal bleeding and renal toxicity. The professional labeling is not included with the OTC packaging or on the OTC product labeling. The professional labeling does, however, permit the maker of an aspirin product to detail the professional labeling to health care providers. Non-aspirin salicylates have a small share of the OTC market. The OTC labeling of these products is similar to aspirin. They do not, however, have the professional labeling of aspirin. Currently, three NSAIDs are available for OTC use as analgesics. Ibuprofen has been available since 1984; naproxen sodium since 1994; and ketoprofen since 1996. However, the years of experience with all of these drugs are longer when considering the prescription use. When these products were switched to OTC marketing for the relief of minor aches and pains, there were discussions regarding the types of warning statements that should be carried from the prescription label to the OTC label. At the time of the switches, the Agency decided not to include any organ specific warnings. In the prescription NSAID labels and the professional label for aspirin, warnings are listed for gastrointestinal and renal problems. The current OTC labels for aspirin and NSAIDs places a limit of 10 days of continuous use. The labeling refers the consumer to their doctor for advice if it is to be used for longer periods of time. On this day, we will ask you to consider if additional risk management strategies are needed to alert the OTC consumer with regard to gastrointestinal bleeding and renal toxicity.

Points for Committee Discussion

1. The prescription labeling for NSAIDs and the professional labeling for aspirin have warnings for gastrointestinal bleeding and possible renal toxicity. Aside from the alcohol warning required on all NSAID and aspirin products, the current OTC labels do not have organ specific warnings. Given the information provided today, please discuss the relative risks for gastrointestinal bleeding and renal toxicity associated with the use of OTC doses of NSAIDs or aspirin.

For gastrointestinal bleeding:

- a. Describe the relative risk of gastrointestinal bleeding for consumers who use the maximum recommended daily OTC dose of NSAIDs or aspirin.
- b. Are there sub-populations of consumers who are at a greater risk for developing bleeding with OTC doses?

For renal toxicity:

- c. Describe the relative risk of renal toxicity for consumers who use the maximum recommended daily OTC dose of NSAIDs or aspirin.
 - d. Are there sub-populations of consumers who are at a greater risk for developing renal toxicity with OTC doses?
2. Based on your discussion in #1, should additional warnings or other risk management strategies be considered for NSAIDs or aspirin?
 - a. For gastrointestinal bleeding?
 - b. For renal toxicity?

If additional warnings are recommended, please discuss whether the additional warnings should simply inform of the risk or whether they should provide information on the at-risk populations or provide information on symptoms that may alert the consumer of toxicity.

3. Aspirin is somewhat unique in that there is professional labeling for an OTC product. Doctors often instruct patients to purchase OTC aspirin to be used on a chronic basis for cardiovascular and rheumatologic indications. Given that the professional labeling has numerous warnings related to these uses, should any of these warnings be conveyed to the consumer as part of the OTC label? If yes, which warnings and how should they be conveyed to the consumer as part of the OTC label?
4. Are any additional studies needed to evaluate the issues further? Consider:
 - a. Evaluation of revised labeling.
 - b. Studies to further evaluate sub-populations at risk for serious adverse events.
5. Should the labels and packaging of these products more prominently state
 - a. That the product contains aspirin or the specific NSAID?
 - b. That these products should not be used concomitantly with any other NSAID or aspirin product?