

# **Points for Discussion**

## **Nonprescription Drugs Advisory Committee**

**September 19, 2002**

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

### **Issue: Unintentional Acetaminophen Hepatotoxicity**

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 expert 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 continues to believe that acetaminophen is a safe and effective OTC analgesic that benefits tens of millions of consumers every year. Acetaminophen is an important OTC analgesic given its demonstrated lack of potential for causing GI or other bleeding and no known risk of Reye's Syndrome in children. But it is also true that acetaminophen products, as currently labeled and used, are associated with rare reports of unintentional overdose that may lead to serious hepatotoxicity. The issue of hepatotoxicity in association with acetaminophen use is not new and this issue was discussed in the panel report published in 1977. The purpose of today's meeting is to revisit this issue in the context of data on unintentional overdose and determine whether additional measures should be taken to further decrease the risk of these events. The committee, after reviewing the available information, will be asked to discuss factors and circumstances that may contribute to these adverse events and to help determine, as appropriate, additional risk management efforts.

Acetaminophen is currently available in numerous combination and single ingredient OTC products. Within each group of products, a variety of formulations are marketed. The FDA has oversight of the required labeling for OTC products but does not oversee their marketing and advertising. This responsibility lies with the Federal Trade Commission. Acetaminophen is also available in many prescription products. Currently, there are almost two hundred approved New Drug Applications (NDA) or abbreviated New Drug Applications (ANDA) for products that contain acetaminophen in combination with a narcotic analgesic. FDA regulates the labeling and advertising of these products; however, FDA does not regulate the practice of pharmacy, nor the type of information placed on the dispensing container by the pharmacist.

## **Points for Committee Discussion**

1. Cases of unintentional acetaminophen overdose and associated hepatotoxicity have been reported to the FDA and other adverse events databases, and have been reported in the medical literature. In some of these cases it appears that consumers/patients used two or more acetaminophen containing products (OTC and/or prescription) simultaneously, each at or near the maximum recommended dose. For many of these medication errors, it is not possible to discern from the reports why the consumer/patient took two products containing acetaminophen.
  - a. Discuss possible factors or circumstances that may contribute to these events?  
Examples of possible factors could include, but are not limited to, the following:
    - failure of consumers to recognize the types of ingredients in OTC products and/or the potential harm of exceeding the recommended dose
    - the wide variety of products available both OTC and by prescription that contain acetaminophen (e.g. combination, single ingredient, multiple formulations)
    - the lack of consumer understanding of the potential adverse consequences of taking two different products containing acetaminophen simultaneously
    - the clarity of labeling of ingredients on the immediate container provided to the patient for prescription product containers containing acetaminophen.
  
2. There are many factors identified in the medical literature that appear to be associated with an increased risk for acetaminophen hepatotoxicity. In some of the case reports of acetaminophen-associated hepatotoxicity it appears that the patient ingested a dose only slightly above the recommended maximum daily dose of acetaminophen for several days and then developed serious hepatotoxicity. Assuming that the dosing information in these reports is accurate, this suggests that some individuals may be more susceptible to acetaminophen-induced hepatotoxicity.
  - a. Are there identifiable underlying factors or sub-populations that may make some individuals more susceptible to hepatic toxicity (e.g. underlying liver disease, malnutrition, drug interactions, and alcohol users)?
  
  - b. If there are identifiable sub-populations at increased risk of acetaminophen-induced hepatotoxicity, what reasonable measures could be taken to decrease the risk for each sub-population? Possible measures could include but are not limited to the following:
    - adjustment of maximum total daily dose or dosing interval
    - changes in labeling that identify and highlight the risk (e.g. organ-specific warnings)
    - additional research on specific sub-populations
    - consumer and physician education.

3. A fair proportion of AERS cases reporting hepatotoxicity occurs with the use of prescription combination (narcotic/acetaminophen) products. Many of these cases involve patients with underlying histories of alcohol abuse and/or substance abuse.
  - a. What additional measures can be taken to better insure that prescribers and patients are more aware of this potential risk?
  
4. Inadequate pain management with either OTC or prescription medications appears to be a factor for some individuals to take more than the recommended daily dose. The OTC products already have instructions regarding the maximum daily dose permitted. This, however, does not preclude individuals from either not reading or understanding these instructions or they ignore these instructions all together. The prescription products, dispensed by a pharmacy, may not include information on the maximum daily dose on the container although this information is available in most prescription labeling.
  - a. What measures should the agency consider to reinforce the message that exceeding the recommended dose can lead to toxicity for both OTC and prescription products?

For OTC products, possible measures could include but are not limited to the following:

- Consumer Education
- Changes on the labeling that identify and highlight the risk
- Packaging that enhances appropriate use
- Consumer insert

For prescription products, possible measures could include but are not limited to the following:

- Unit of use packaging with labeling on each blister pack
- Physician and pharmacist education
- Publication of information in professional journals
- Initiate physician and consumer educational campaign
- FDA publication which identifies and highlights the danger and risk
- Patient information leaflet and stickers on prescriptions at time of dispensing

5. Are additional studies needed to evaluate the issues further? Consider:
  - a. Evaluation of the effectiveness of educational programs
  - b. Evaluation of revised labeling
  - c. Surveillance of serious acetaminophen hepatotoxicity cases
  - d. Enhanced collection of information when medication errors occur
  - e. Better understanding of consumer use of these products