

MEMORANDUM

DATE: April 27, 2007

TO: U.S. FOOD AND DRUG ADMINISTRATION

FROM: AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD)

RE: PUBLIC COMMENT REGARDING THE PROPOSED AMENDMENT OF THE TENTATIVE FINAL MONOGRAPH ON INTERNAL ANALGESIC, ANTIPYRETIC AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE (Docket no. 1977N-0094L)

The American Association for the Study of Liver Diseases (AASLD) has reviewed the Food and Drug Administration's (FDA) proposal to amend its over-the-counter (OTC) labeling regulations and the tentative final monograph (TFM) for OTC internal analgesic, antipyretic, and anti-rheumatic (IAAA) drug products (Federal Register Vol.71, No.247, Tuesday, December 26, 2006).

The AASLD is fully supportive of the agency's conclusion that acetaminophen hepatotoxicity is an important public health consideration and that additional labeling is necessary for the drug to continue to be generally recognized as safe and effective.

Furthermore, the AASLD fully supports the FDA's proposal to improve labeling of acetaminophen-containing OTC products to ensure consumer awareness of the following items:

- That a product contains acetaminophen
- That acetaminophen can cause severe or even fatal liver injury
- That active alcohol consumption can increase the risk of liver injury from acetaminophen
- That dosing for children should be very carefully reviewed to ensure that proper formulations are used in an amount appropriate for age and body weight

The AASLD applauds FDA's plans to continue an educational campaign to consumers and health care providers regarding the risks associated with acetaminophen use.

In Section XIV. of the Federal Register, FDA requested specific comment on the following items:

1. Both comment and data on whether adult NSAID products should contain a warning regarding fluid loss or dehydration similar to children's NSAID products.

AASLD offers no comment on this issue.

2. Appropriate approaches to reduce unintentional acetaminophen overdose.

AASLD notes that 63% of unintentional acetaminophen overdoses in the U.S. occur in persons taking acetaminophen-narcotic combinations.¹ AASLD therefore offers two recommendations to reduce the risk of unintentional acetaminophen overdose:

- Eliminate acetaminophen-narcotic combination drugs completely from the market. This is the preferred strategy, because data are weak regarding the synergistic effects of acetaminophen-narcotic combinations. The risk of hepatotoxicity greatly outweighs the theoretical benefit of these preparations in the management of pain. Such steps are already being taken in the United Kingdom with acetaminophen-dextropropoxyphene combinations.²
- Alternatively, were the FDA to permit the continued use of acetaminophen-narcotic combinations, AASLD recommends that the dose of acetaminophen in these combinations be restricted to 325 mg per tablet or capsule.

3. Whether more specific directions, such as those currently required for OTC drug products containing ibuprofen, should be considered for acetaminophen.

AASLD recommends that FDA consider the following specific directions or warnings for acetaminophen:

This product can cause severe or even fatal liver injury. The chance is higher if you:

- *Use this drug at the maximum recommended dose (4 grams/day) for 5 or more consecutive days,*
- *Use this drug simultaneously with other drugs containing acetaminophen*
- *Use this drug simultaneously with certain prescription medications (isoniazid, phenobarbital, warfarin)*
- *Use this drug at the maximum recommended dose (4 grams/day) when food intake is restricted or prohibited*
- *Use more than 2 grams/day of this drug while drinking alcohol*
- *Have an ongoing serious liver condition*

4. Both comment and data on whether there are specific populations of people for whom the maximum daily dose for acetaminophen is not safe and effective and should be lowered.

Maximum safe dose for all persons. AASLD notes a recent study demonstrating that 50% of healthy volunteers who took 4 grams of acetaminophen daily for 14 days developed ALT elevations > 2 X ULN.³ 38% of patients in the same study developed ALT elevations > 3 X normal, and in 23%, ALT rose to > 5 X ULN. The risk of hepatotoxicity was similar whether acetaminophen was consumed alone or together with a prescription narcotic (oxycodone, hydromorphone, morphine). The subjects in this study did not consume ethanol and had no evidence of underlying liver disease. These findings support the notion that 4 grams per day is the maximum safe daily dose for any person, even one in good health.

Whether these findings warrant a reduction in the maximum recommended daily dose of acetaminophen to from 4 g to 3 g is currently unclear. Nevertheless, the data indicate that acetaminophen has a narrow therapeutic-to-toxic window, and that regular use of the drug leads to subclinical liver damage much more frequently than previously appreciated. AASLD

notes that reducing the maximum daily dose of acetaminophen to 3 g may add a measure of increased safety for all patients, including those with chronic liver disease or alcoholism.

Maximum safe dose for persons with underlying liver disease. AASLD acknowledges the data presented by the FDA indicating a possible increased risk of acetaminophen-induced liver injury in individuals with underlying liver disease (Federal Register Section IV.). AASLD cautions, however, that cytochrome P450 activity is extremely variable in the setting of liver disease and that levels and activities of P450 isoforms depend upon the etiology as well as the severity of disease.⁴⁻⁶ AASLD believes acetaminophen can be used safely in patients with liver disease, provided the maximum daily dose in this population does not exceed 2 g/day. AASLD recognizes that this recommendation is incompletely supported by experimental data, and calls for additional research to determine which (if any) subgroups of patients with liver disease are at increased risk of liver injury from standard acetaminophen use.

5. Both comment and data on specific dosage for safe and effective use of acetaminophen in people who consume alcohol.

AASLD believes that the proposed maximum daily dose of acetaminophen (4 g/day) is inappropriately high for regular consumers of alcohol and recommends 2 g/day as the maximum daily dose for this group. This position is based on evidence that 10% of patients (15/151) who developed acute liver failure from concurrent acetaminophen and alcohol use took less than 4 g acetaminophen per day.¹ These findings are consistent with previous comments received by the FDA as well as data noted by the FDA and NDAC suggesting that some active alcohol users with severe acute liver injury reported consuming between 2-4 g of acetaminophen per day. Although it is unknown what proportion of individuals who consume 2-4 g of acetaminophen per day concurrently with alcohol will develop severe liver injury, the fact that some cases of life-threatening illness do occur is sufficient to make this recommendation. Studies that purported to show the safety of 4 g/day in recovering alcoholics were very limited in scope and duration.⁷

6. Both comment and data on whether combinations of acetaminophen with NAC or methionine would prevent or reduce acetaminophen-induced liver toxicity.

AASLD reviewed the U.K. experience with 500 mg acetaminophen:100 mg methionine combinations (Pameton, Paradote). Although data are encouraging that such preparations would deter intentional overdoses,⁸ the potential risk of exposing the general population to supplemental methionine intake is unknown. There is a theoretical concern that regular methionine ingestion could increase plasma homocysteine levels and predispose to cardiovascular disease. At the doses contained within a 5:1 combination drug, however, this is unlikely. A more practical concern is that combining acetaminophen with methionine would substantially increase the cost of the drug (prices for the combination in the U.K. are 6 times higher than that for acetaminophen alone).⁹ A combination drug would not be purchased by consumers unless the cost was competitive with that of other pain relievers.

AASLD concurs with FDA that there is insufficient information to judge the actual liver-related benefit of combining acetaminophen with either NAC or methionine. AASLD endorses the need for further research in this area to determine the impact of combined regimens on the incidence of acetaminophen-induced hepatotoxicity.

7. Both comment and data on package size or package configuration limitations on the sale of acetaminophen.

AASLD points to recent data from the FDA's Center for Drug Evaluation and Research indicating that fatalities in the U.S. from acetaminophen overdoses are increasing and now total 458 per year (100 unintentional).¹⁰ AASLD emphasizes that efforts in the United Kingdom to reduce acetaminophen package size have significantly reduced admission rates to hospitals and liver specialty units.¹¹⁻¹⁶ This improvement has been attributed to a decrease in the number of intentional overdoses as well as the number of capsules or tablets taken in an intentional overdose.¹¹ Importantly, package size limitation has had little impact on the incidence of acetaminophen hepatotoxicity in Scotland. The reason is that such restrictions did not curtail the availability and prescription of acetaminophen-dextropropoxyphene combinations (co-proxamol or Darvocet®).¹⁷ Recognizing that this combination drug is now the leading cause of acetaminophen-induced hepatotoxicity in the United Kingdom, the government is removing co-proxamol from the market.²

In aggregate, these data indicate that reducing package size and changing package configuration (to blister packs) has the potential to significantly reduce the number of cases of acetaminophen hepatotoxicity in the U.S. The only caveats are that blister packs are not uniformly child-proof¹⁸ and that reducing acetaminophen availability may increase the use of other potentially dangerous antipyretics or analgesics without size restrictions (e.g., NSAIDs).¹⁵ Regarding the latter, data from the U.K. do not demonstrate any increase in the number of fatalities from alternate agents after implementing restrictions on acetaminophen. They do, however, indicate that regulation of acetaminophen was followed by a modest increase in the number of non-fatal NSAID overdoses.¹⁹

8. Both comment and data on whether acetaminophen poses additional risk for certain population subgroups (e.g., conditions in which GSH is reduced).

AASLD acknowledges the potential for certain co-morbid conditions to modify the risk of acetaminophen hepatotoxicity (e.g., prolonged fasting, anorexia nervosa, bulimia and malnutrition, advanced HIV infection).²⁰⁻²² Whether these conditions represent risk factors because of insufficient GSH or because they unmask other (genetic) predispositions to acetaminophen toxicity is unknown.²³ Further research is required to clarify this issue.

9. Both comment and data on whether additional labeling is necessary regarding acetaminophen-warfarin drug-drug interaction.

Although AASLD acknowledges prior controversy regarding the risk of acetaminophen use in patients taking warfarin,²⁴⁻²⁶ it notes a recent randomized, double-blind, placebo-controlled study in which patients on stable warfarin doses for >1 month were given 4 g of acetaminophen daily for 14 days.²⁷ Acetaminophen treatment caused a significant rise in INR over this 2-week interval compared to placebo (INR = 3.45 for acetaminophen vs. 2.66 for placebo at 14 days). Thus, AASLD recommends a warning statement regarding the use of acetaminophen with warfarin, in addition to certain other drugs such as phenobarbital and isoniazid. These drug-drug interaction warnings should be placed both on the package insert and in the cautions section on the back of the package (see # 3).

10. Comment on the proposal to include a warning on acetaminophen products for patients with liver disease to ask their doctor for advice. Also, request information

and data on the current dosing practices of health providers who treat patients with underlying liver disease.

“Ask your doctor” warning for patients with liver disease. AASLD believes FDA has made a sound argument for its proposal to require warnings on acetaminophen products to “ask a doctor before use if [*you; the child; the user*] has liver disease.” This general statement will alert liver disease patients to a potential risk without advising indiscriminately that they either avoid acetaminophen or limit use to a predetermined dose. Such an open-ended warning will permit health care providers to counsel liver disease patients about acetaminophen on a case-by-case basis. The proposed language is appropriate based upon the data reported in Section IV. of the Federal Register.

Current provider dosing practices for patients with liver disease. AASLD reports that hepatologists commonly prescribe low doses of acetaminophen for their patients with liver disease (see #4). Most specialists recommend a maximum of 2 g acetaminophen per day for patients with chronic liver disease or cirrhosis (unpublished data). Acetaminophen is actually preferred over non-steroidal anti-inflammatory drugs for patients with advanced liver disease, because the latter agents promote sodium retention and increase the risk of hepatorenal syndrome and renal failure.

As evidence of its confidence in the safety and efficacy of 2 g/d acetaminophen, AASLD notes that its own Practice Guideline on the Treatment of Chronic Hepatitis C specifically calls for the use of acetaminophen (up to 2 g/day) or non-steroidal anti-inflammatory agents to manage the influenza-like side effects of interferon therapy.²⁸

In conclusion, AASLD notes that:

1. Acetaminophen hepatotoxicity in the United States exceeds that of all prescription drugs combined.^{1, 29}
2. More than four years have passed since the last Non-Prescription Drug Advisory Committee meeting (September 19, 2002), and it is appropriate for the issues surrounding acetaminophen toxicity to be readdressed with another advisory committee meeting as part of an overall policy update.
3. The agenda for such an advisory committee meeting should include not only package labeling, but also a discussion about revising and possibly restricting the use of OTC and prescription narcotic-acetaminophen preparations, given the information now available regarding the benefit of such risk reduction practices in other nations (see #7).

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