



## **AMERICAN PAIN FOUNDATION SHARES ACETAMINOPHEN TASK FORCE'S CONCERNS OVER RECENT FDA ADVISORY COMMITTEE RECOMMENDATIONS REGARDING OVER-THE-COUNTER ACETAMINOPHEN MEDICATIONS**

### **Background**

On June 29 and 30, 2009, the United States Food and Drug Administration (FDA) held an Advisory Committee meeting regarding liver injury related to acetaminophen use in both over-the-counter (OTC) and prescription medicines. The Advisory Committee voted in favor of a number of potential changes<sup>1</sup>, which will have far-reaching implications for Americans in pain and those providing their care. These include:

- reduction of the maximum recommended daily dose of acetaminophen
- reduction of the maximum recommended single dose of acetaminophen

Of great concern was the lack of scientific evidence presented to support the recommendations of the Advisory Committee. The briefing documents were less than robust and several panel members commented on insufficient data. Specifically, Dr. Judith Kramer, Advisory Committee member, stated "It seems to me that we were limited a lot today by lack of information about effectiveness -- dose-ranging information about effectiveness of acetaminophen for mild to moderate pain. And I think the agency and independent agencies, like the NIH and academics, should be encouraged to do studies, including 325, 500, 600 and 1,000, for the types of pain that are -- that these products are actually used for in practice"<sup>2</sup>. Another Advisory Committee member, Dr. Knox Todd, stated that "I know those of us on the committee have felt a little whip-sawed about some of this information, and it's always difficult to -- to attempt to advise on policy in the lack of complete information"<sup>2</sup>. Recommendations made without full consideration of what is known about acetaminophen's potential for liver injury is dangerous considering unintended consequences of the proposed actions.

In response to the recent Advisory Committee recommendations, the Pain Care Forum<sup>3</sup> has formed an Acetaminophen Task Force composed of its members and other stakeholders regarding liver injury related to acetaminophen.

It is the intent of this Task Force to communicate the concerns regarding the Committee's recommendations to the FDA through submissions to the docket by all interested stakeholders. The docket will close on September 30, 2009. This document is intended to provide an overview of the issues related to the recommendations regarding the over-the-counter acetaminophen medications.

### **Acetaminophen is an important medication**

Acetaminophen is one of the most frequently used medications in the United States<sup>4</sup>.

- Commonly recommended by many treatment guidelines as a first-line therapy for pain and fever, including the recent recommendations from the American Geriatric Society<sup>5</sup>.
- Acetaminophen is often the safest medication for patients, particularly those with contraindications for alternative nonprescription therapies, such as OTC nonsteroidal anti-inflammatory drugs (NSAIDs).
- Millions of Americans rely on this safe and efficacious medication to relieve their pain and fever.

#### **Acetaminophen 4 grams/day (1 grams/dose) is safe and effective**

The Advisory Committee recommendations are based upon an estimated narrow margin of safety, *not* evidence of liver injury with the currently approved maximum dose of 4 g/day.

- The currently approved maximum daily dose has *not* been associated with liver injury. Acetaminophen has been recognized as generally safe and effective for decades and is associated with few adverse effects when taken as directed.
- The much discussed 2006 publication by Watkins et al<sup>6</sup> concluded that “acetaminophen clearly has a remarkable safety record when taken as directed, and chronic treatment with 4 g daily has been confirmed to be safe.”
- During the Advisory Committee meeting, the safety data were summarized by Dr. Robert D. Kerns, a member of the Advisory Committee: “there really are not compelling data to support the idea that there's a greater risk -- that there is specific risk associated with 4 grams per day”<sup>2</sup>.
- The purported narrow threshold is based upon retrospective patient reports of acetaminophen exposure. The case reports used to support the idea of a narrow therapeutic margin involved impaired patients as well as those that have social and behavioral factors consistent with underestimation of dose. These data are questionable at best and should be interpreted with caution. Furthermore, additional studies should gather empirical data on which to establish a true safety margin.
- According to a report from the FDA’s Center for Drug Evaluation and Research (“CDER”) in which 100 deaths associated with acetaminophen were analyzed, 82% were the result of suicide or intentional misuse<sup>7</sup>. In all of these cases, decreasing the dosage would not have had an impact on preventing this outcome.

#### **Efficacy of current dosing regimens has been demonstrated.**

- Studies have shown that 500 mg, 650 mg and 1000 mg doses are efficacious for pain relief and fever reduction.
- The limited data available do suggest increased efficacy with the 1000 mg dose. As summarized by Dr. Robert D. Kerns, an Advisory Committee member, during the second day of the Advisory Committee meeting: “the only two studies that were presented that ... were specifically powered to directly compare a dose of 1,000 milligrams versus a lower dose found support for increased efficacy of the higher dose”<sup>2</sup>.

#### **Implications of Significantly Reducing the Dose of Acetaminophen Available Without a Prescription**

Unintended consequences resulting from a reduction of the single nonprescription acetaminophen dose or the maximum daily nonprescription dose can be anticipated.

- A reduction in the single nonprescription acetaminophen dose from the current 1000 mg will lead to ineffective pain relief in some patients. In response, these patients will likely take more of the same medication, switch to alternative therapies, or both. This could heighten the potential for unintentional overdose as well as lead to the use of alternative therapies known to be associated with increased risk.
- The same concerns arise with reduction of the maximum daily dose of acetaminophen from the current 4 g/day. One cannot expect patients to live with inadequate pain relief. If people

experience inadequate pain relief they will seek other options, many of which will be more toxic than acetaminophen.

- Limiting the 1000 mg single dose to prescription will increase the burden on patients and the already strained healthcare system. For some patients, particularly the increasing population of uninsured Americans, the hurdle to obtain a prescription will result in insufficient pain relief for which less safe OTC medications or additional acetaminophen (above recommended labeled dose) will be taken.
- In any case, the most logical alternative nonprescription therapy would be OTC NSAIDs. Incidence of NSAID toxicity would be expected to increase. NSAID toxicity, both in the acute and chronic setting, has been associated with gastrointestinal bleeding, perforation and obstruction, cardiovascular thrombotic events, renal toxicity, anaphylactic reactions, serious skin reactions as well as hepatic toxicity. It is unlikely, then, that an overall reduction in harm to patients would occur, but simply a shift in the types and seriousness of adverse events.

### **Recommendations for Alternative Actions to Address Health Concerns**

We strongly support regulatory initiatives which strive to protect patients and ensure the safety of medications. However, it is unclear how the proposed recommendation to reduce the single and daily doses of nonprescription acetaminophen will result in the intended effect of reducing hepatic injury related to overuse of these medications while preserving the utility for those that use it appropriately. Rather, we offer the following recommendations as alternative options for preventing unintentional acetaminophen overdose which is related to hepatic injury.

- Changes in product labeling
  - The Final Labeling Rule effective April 2009 already incorporates changes to ensure the presence of acetaminophen is clearly marked in OTC analgesics, antipyretics, and antirheumatics and appropriate organ specific warnings are listed<sup>8</sup>. These same regulations should apply to prescription acetaminophen-containing medications.
  - Change dosing instructions to read “Take 1 or 2 tablets/caplets”. This will encourage patients to use the lowest effective dose. This change was suggested by one of the sponsors at the Advisory Committee meeting yet the proceedings did not allow for the committee to vote on such change.
  - Standardize labels on all medications containing acetaminophen to include a clearly understood and standardized icon or pictograph conveying both the ingredient (i.e., acetaminophen) as well as maximum single and daily dose limits on use.
  - Labeling should unequivocally state that severe liver injury can result from improper acetaminophen use.
- Changes in product packaging
  - Innovative packaging techniques aimed at reducing the amount of acetaminophen available at one time already exist, some of which were presented by one of the sponsors at the Advisory Committee meeting.
- Develop and implement targeted education campaigns directed at both consumers and healthcare practitioners. Both campaigns should be delivered through various channels to maximize reach and to enhance comprehension and compliance. The campaigns would introduce the new labeling, packaging and the icon/pictograph. These campaigns would clearly present the known risks of acetaminophen use and overuse.
- Collaboration among sponsors, regulatory agencies, academia, professional organizations and patient advocate groups to gather empirical data to be considered prior to decision making.

- The underlying concern at the Advisory Committee meeting was the lack of meaningful data to make sound recommendations. The committee members identified several issues that require additional research to better understand both the extent of the problem and appropriate solutions. Such issues include, but are not limited to: the comparison of efficacy between 1000 mg dose and the proposed lower dose, unintended consequences associated with reduction in maximum single and daily nonprescription acetaminophen doses, and true threshold dose associated with increased risk of hepatic injury.

<sup>1</sup> [Questions and Vote Results for the June 29-30, 2009 Joint Meeting of the Drug Safety and Risk Management Advisory Committee with the Anesthetic and Life Support Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee.](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM170188.pdf)  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM170188.pdf>

<sup>2</sup> Meeting Transcript for the June 30, 2009 Joint Meeting of the Drug Safety and Risk Management Advisory Committee with the Anesthetic and Life Support Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee.  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM174699.pdf>

<sup>3</sup> The Pain Care Forum is a group of over 50 organizations---professional associations, consumer organizations, industry members and others---which focuses on pain policy issues. It was formed by the American Pain Foundation and other organizations to combat the fragmentation of knowledge and effort that exists in the pain community. Its goals are to provide a forum for the exchange of information and ideas about pain policy and legislation and support collaborative actions on common issues of concern.

<sup>4</sup> Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA* 2002; 287:337-44. See also <http://www.bu.edu/slone/SloneSurvey/SloneSurvey.htm>

<sup>5</sup> American Geriatrics Society. Pharmacological management of persistent pain in older persons. *Journal of American Geriatrics Society* 2009; 57:1331-46.

<sup>6</sup> Watkins PB et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily. *JAMA* 2006; 296:87-93.

<sup>7</sup> "Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee; Notice of Meeting," *Federal Register* 74:78 (24 April 2009) p. 18731.

<sup>8</sup> United States Food and Drug Administration. *Federal Register* 2009, Docket No. FDA1977N0013 (formerly Docket No. 1977N0094L).

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