FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure

Safety Announcement

[1-13-2011] The U.S. Food and Drug Administration (FDA) is asking drug manufacturers to limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids. This action will limit the amount of acetaminophen in these products to 325 mg per tablet, capsule, or other dosage unit, making these products safer for patients.

In addition, a *Boxed Warning* highlighting the potential for severe liver injury and a *Warning* highlighting the potential for allergic reactions (e.g., swelling of the face, mouth, and throat, difficulty breathing, itching, or rash) are being added to the label of all prescription drug products that contain acetaminophen.

These actions will help to reduce the risk of severe liver injury and allergic reactions associated with acetaminophen.

Acetaminophen is widely and effectively used in both prescription and over-the-counter (OTC) products to reduce pain and fever. It is one of the most commonly-used drugs in the United States. Examples of prescription products that contain acetaminophen include hydrocodone with acetaminophen (Vicodin, Lortab), and oxycodone with acetaminophen (Tylox, Percocet).

OTC products containing acetaminophen (e.g., Tylenol) are not affected by this action. Information about the potential for liver injury is already required on the label for OTC products containing acetaminophen. FDA is continuing to evaluate ways to reduce the risk of acetaminophen related liver injury from OTC products. Additional safety measures relating to OTC acetaminophen products will be taken through separate action, such as a rulemaking as part of the ongoing OTC monograph proceeding for internal analgesic drug products.

Additional Information for Patients

- Acetaminophen-containing prescription products are safe and effective when used as directed, though all medications carry some risks.
- Do not stop taking your prescription pain medicine unless told to do so by your healthcare professional.
- Carefully read all labels for prescription and OTC medicines and ask the pharmacist if your prescription pain medicine contains acetaminophen.
- Do not take more than one product that contains acetaminophen at any given time.
- Do not take more of an acetaminophen-containing medicine than directed.
- Do not drink alcohol when taking medicines that contain acetaminophen.
- Stop taking your medication and seek medical help immediately if you:
  - Think you have taken more acetaminophen than directed or
  - Experience allergic reactions such as swelling of the face, mouth, and throat, difficulty breathing, itching, or rash.
- Report side effects to FDA's MedWatch program using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

The maximum amount of acetaminophen in a prescription tablet, capsule, or other dosage unit will be limited to 325 mg. However, the total number of tablets or capsules that may be prescribed and the time intervals at which they may be prescribed will not change as a result of the lower amount of acetaminophen. For example, for a product that previously contained 500 mg of acetaminophen with an opioid and was prescribed as 1-2 tablets every 4-6 hours, once reformulated to contain 325 mg of acetaminophen, the dosing instructions can remain unchanged.

- Advise patients not to exceed the acetaminophen maximum total daily dose (4 grams/day).
- Severe liver injury, including cases of acute liver failure resulting in liver transplant and death, has been reported with the use of acetaminophen.
- Educate patients about the importance of reading all prescription and OTC labels to ensure they are not taking multiple acetaminophen-containing products.
- Advise patients not to drink alcohol while taking acetaminophen-containing medications.

- Rare cases of anaphylaxis and other hypersensitivity reactions have occurred with the use of acetaminophen.
- Advise patients to seek medical help immediately if they have taken more acetaminophen than directed or experience swelling of the face, mouth, and throat, difficulty breathing, itching, and rash.
- Report adverse events to FDA's MedWatch program using the information in the "Contact Us" box at the bottom of the page.

Data Summary and Discussion

A number of studies have tried to answer the question of how common liver injury is in relation to the use of acetaminophen. Although many questions remain about the full scope of the problem, the following examples indicate what is known about the extent of liver failure cases reported in the medical literature and clearly indicates a reason for concern:

- From 1998 to 2003, acetaminophen was the leading cause of acute liver failure in the United States, with 48% of acetaminophen-related cases (131 of 275) associated with accidental overdose.[1]
- A 2007 Centers for Disease Control and Prevention (CDC) population-based report estimates that, nationally, there are 1600 cases of acute liver failure (ALF) each year (all causes). Acetaminophen-related ALF was the most common etiology.[2]
- Summarizing data from three different surveillance systems, there were an estimated 56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths related to acetaminophen-associated overdoses per year during the 1990-1998 period.[3]
- In a study that combined data from 22 specialty medical centers in the United States, acetaminophen-related liver injury was the leading cause of ALF for the years 1998 through 2003.[1] This study also found that a high percentage of cases of liver injury due to acetaminophen were related to unintentional overdose, in which the patient mistakenly took too much acetaminophen. This finding was confirmed in a later study (2007).[2] Many other cases of acute liver injury are caused by intentional overdoses of acetaminophen (i.e., associated with self-harm).
- Across various studies, consumers were found to have taken more than the recommended dose when using an OTC product, a prescription product, or both. The Toxic Exposure Surveillance System (TESS), now named the National Poison Data System (NPDS), which captures data from calls to 61 poison control centers, provides additional data on acetaminophen overdose and serious injury. In 2005, TESS showed that calls about poisoning cases that resulted in major injury numbered 1,187 for OTC single-ingredient products, 653 for OTC combination products, and 1,470 for prescription-opioid combination products.[4]

The risk of liver injury associated with the use of acetaminophen was discussed at the Joint Meeting of the FDA Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and Anesthetic and Life Support Drugs Advisory Committee, held on June 29-30, 2009 (for complete safety reviews and background information (http://wayback.archive-it.org/7993/20161022142731/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdviso
(http://www.fda.gov/about-fda/website-policies/website-disclaimer) discussed at this meeting).

The Advisory Committee recommended a range of additional regulatory actions such as adding a boxed warning to prescription acetaminophen products, withdrawing prescription combination products from the market, or reducing the amount of acetaminophen in each dosage unit. FDA considered the Committee's advice for OTC products when deciding to limit the amount of acetaminophen per dosage unit in prescription products.

By limiting the maximum amount of acetaminophen in prescription products to 325 mg per dosage unit, patients will be less likely to overdose on acetaminophen if they mistakenly take too many doses of acetaminophen-containing products.

For more information on safety considerations for acetaminophen, visit the following link on the FDA web site: Acetaminophen Information (/drugs/information-drug-class/acetaminophen-information)

Table

List of Marketed Acetaminophen-Containing Prescription Products (products affected by the new dosage unit limits are in italics)

1-14-2014: This list was accurate at the time this Drug Safety Communication was published on 1-13-2011; however, it is no longer accurate. FDA intends to publish a new list once the withdrawals currently in process of combination drug products containing more than 325 mg acetaminophen per dosage unit are finalized.

The label may not spell out the whole word or may have an abbreviation, such as “APAP, AC, Acetaminophn, Acetaminoph, Acetaminop, Acetamin or Acetam. “

Brand Name	Generic Name	Dosage Form	Strength
No Current Brand Name	Acetaminophen; Aspirin; Codeine Phosphate	Capsule; Oral	150mg; 180mg; 30mg

No Current Brand Name	Acetaminophen; Codeine Phosphate	Solution; Oral	120mg/ 5mL; 12mg/ 5mL
No Current Brand Name	Acetaminophen; Codeine Phosphate	Tablet; Oral	300mg; 15mg
Capital and Codeine	Acetaminophen; Codeine Phosphate	Suspension; Oral	120mg/ 5mL; 12mg/ 5mL
Tylenol W/ Codeine No. 3	Acetaminophen; Codeine Phosphate	Tablet; Oral	300mg; 30mg
Tylenol W/ Codeine No. 4	Acetaminophen; Codeine Phosphate	Tablet; Oral	300mg; 60mg
No Current Brand Name	Acetaminophen; Butalbital; Caffeine	Tablet; Oral	325mg; 50mg; 40mg
Fioricet	Acetaminophen; Butalbital; Caffeine	Tablet; Oral	325mg; 50mg; 40mg
No Current Brand Name	Acetaminophen; Butalbital; Caffeine; Codeine Phosphate	Capsule; Oral	325mg; 50mg; 40mg; 30mg
Fioricet w/ codeine	Acetaminophen; Butalbital; Caffeine; Codeine Phosphate	Capsule; Oral	325mg; 50mg; 40mg; 30mg
Phrenilin with Caffeine and Codeine	Acetaminophen; Butalbital; Caffeine; Codeine Phosphate	Capsule; Oral	325mg; 50mg; 40mg; 30mg
Anexsia 5/ 325	Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	325mg; 5mg
Anexsia 7.5/ 325	Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	325mg; 7.5mg
No Current Brand Name	Acetaminophen; Hydrocodone Bitartrate	Solution; Oral	325mg/ 15mL; 10mg/ 15mL
No Current Brand Name	Acetaminophen; Hydrocodone Bitartrate	Solution; Oral	325mg/ 15mL; 7.5mg/ 15mL
No Current Brand Name	Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	300mg; 10mg
No Current Brand Name	Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	300mg; 5mg
No Current Brand Name	Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	300mg; 7.5mg
Norco	Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	325mg; 10mg
Norco	Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	325mg; 5mg
Norco	Acetaminophen; Hydrocodone Bitartrate	Tablet; Oral	325mg; 7.5mg
Oxycet	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325mg; 5mg
No Current Brand Name	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	300mg; 10mg
No Current Brand Name	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	300mg; 2.5mg
No Current Brand Name	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	300mg; 5mg
No Current Brand Name	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	300mg; 7.5mg
Percocet	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325mg; 10mg
Percocet	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325mg; 2.5mg
Percocet	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325mg; 5mg
Percocet	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325mg; 7.5mg
Roxicet	Acetaminophen; Oxycodone Hydrochloride	Solution; Oral	325mg/ 5mL; 5mg/ 5mL
Roxicet	Acetaminophen; Oxycodone Hydrochloride	Tablet; Oral	325mg; 5mg
Ultracet	Acetaminophen; Tramadol Hydrochloride	Tablet; Oral	325mg; 37.5mg

References

1. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, et al. Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005; 42:1364-72.
2. Bower WA, Johns M, Margolis HS, Williams IT, Bell BP. Population-based surveillance for acute liver failure. *Am J Gastroenterol*. 2007;102:2459-63.
3. Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of acetaminophen (Paracetamol)-associated overdoses in the United States. *Pharmacoepidemiol Drug Saf*. 2006;15:398-405.
4. Lai MW, Klein-Schwartz W, Rodgers GC, Abrams JY, Haber DA, Bronstein AC, Wruk KM. 2005 Annual Report of the American Association of Poison Control Centers' national poisoning and exposure database. *Clin Toxicol*. 2006;44:803-932.

Related Information

- Acetaminophen Information (/drugs/information-drug-class/acetaminophen-information)
- FDA limits acetaminophen in prescription combination products; requires liver toxicity warnings (https://wayback.archive-it.org/7993/20170111224116/http:/www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm239894.htm) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)
- Questions and Answers about Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit (https://wayback.archive-it.org/7993/20170111224115/http:/www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm239871.htm) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)
- List of Marketed Acetaminophen-Containing Prescription Products (https://web.archive.org/web/20130404083830/http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm239874.htm) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)
- 2009 Meeting Materials, Drug Safety and Risk Management Advisory Committee (https://wayback.archive-it.org/7993/20170111202406/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvi (http://www.fda.gov/about-fda/website-policies/website-disclaimer)
- FDA Drug Safety Podcast for Healthcare Professionals: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure (https://wayback.archive-it.org/7993/20170111233935/http:/www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm240513.htm) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)