



NATIONAL PBM BULLETIN

June 10, 2014

DEPARTMENT OF VETERANS AFFAIRS PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

ACETAMINOPHEN SAFETY

I. ISSUE

Risk of severe liver damage continues to be a concern with the use of high doses of acetaminophen exceeding the maximum recommended dose of 4,000 milligrams (mg), or 4 grams (g), within a 24-hour period.¹⁻³

II. BACKGROUND

Acetaminophen overdose has become the number one cause of acute liver failure and one of the most common causes of death from acute liver failure.^{4,5} Approximately half of all cases of acetaminophen-related liver failure in the United States ensued from inadvertent overdose of prescription combination drugs containing acetaminophen as an ingredient.^{6,7} Patients who experienced severe liver injury associated with high doses of acetaminophen had the following in common:

- Consumption of more than the prescribed dose of an acetaminophen-containing product in a 24-hour period;¹
- Utilization of multiple acetaminophen-containing product at the same time;¹ or
- Concomitant alcohol use while taking acetaminophen products.¹

Hepatic damage caused by acetaminophen toxicity can manifest as increases in liver enzyme tests to acute liver failure resulting in liver transplant and/or death. In acute acetaminophen overdose, symptoms of hepatotoxicity may be absent or nonspecific in the first 3 to 4 days, making recognition of the problem difficult, particularly in unintentional overdoses.⁸ In instances of chronic or repeated supratherapeutic ingestion (RSTI), which often occurs in patients with acute or chronic pain syndromes taking upwards of 7.5 g of acetaminophen per day, hepatotoxicity may go undiagnosed until after irreversible liver damage has occurred.

III. DISCUSSION

To reduce the risk of accidental acetaminophen overdose and toxicity, the Food and Drug Administration (FDA) has spearheaded numerous changes, over the last three years including:

- Limiting the strength of acetaminophen in *prescription* drug products (mainly combination formulations with opioids);⁷ and
- Adding a *Boxed Warning* highlighting the potential for severe liver injury as well as a *Warning* highlighting the potential for allergic reactions (e.g., swelling of the face, mouth, and throat, difficulty breathing, itching, or rash) to the label of all prescription drug products that contain acetaminophen.⁷

As of January 2014, manufacturers of prescription combination products containing more than 325 mg of acetaminophen per dosage unit should have discontinued marketing these products at the request of the FDA. Restricting the maximum amount of acetaminophen to 325 mg per dosage unit in prescription combination products decreases the likelihood of excessive doses of acetaminophen from either unknowingly taking more than one acetaminophen product or taking more than the recommended dose, leading to toxic events such as acute liver injury. Currently, over-the-counter [OTC] acetaminophen products are not subject to the 325 mg ceiling with respect to dosage form manufacturing, but product labels are already required to include information regarding safety risks such as liver injury associated with high doses.^{1,9-12} As such, OTC acetaminophen strength may vary by formulation and manufacturer but dose still should not exceed 4,000 mg, or 4 g, per day.

IV. PROVIDER RECOMMENDATIONS

- Understand that severe liver injury, including cases of acute liver failure resulting in liver transplant and death, has occurred with the use of high doses of acetaminophen.
- Recognize that risk of liver injury occurs at doses of acetaminophen that exceed the maximum of 4,000 mg, or 4 g, in 24 hours.
- Perform medication reconciliation of prescription and OTC medications (including those for allergy, cough, cold, fever, flu, and sleeplessness) to ensure patients do not exceed the recommended maximum daily dose of acetaminophen (4,000 mg or 4 g/day).
- Consider the amounts of both the acetaminophen and the opioid components in the prescription combination drug product when



NATIONAL PBM BULLETIN

June 10, 2014

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

ACETAMINOPHEN SAFETY

IV. PROVIDER RECOMMENDATIONS *(continued from page 1)*

making individual dosing determinations.

- Prescribe combination drug products that contain 325 mg or less of acetaminophen and effectively taper those that contain more than 325 mg.
- Educate patients about the importance of reading all prescription and OTC labels to ensure they do not take multiple acetaminophen-containing products.
- Advise patients not to exceed the acetaminophen maximum total daily dose (4,000 mg or 4 g/day). When in doubt, patients should not try to calculate their total amount of acetaminophen taken each day, but should discuss their daily dose with their pharmacist.
- Instruct patients not to drink alcohol while taking acetaminophen-containing medications.
- Continue to report any adverse reactions with the use of acetaminophen drug products by entering the information into CPRS' Allergies/Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (by phone: 1-800-FDA-1088, fax: 1-800-FDA-0178, online at: <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm> , or by mail).

V. REFERENCES

1. 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. 1-13-2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm> .
2. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, Reisch JS, Schiødt FV, Ostapowicz G, Shakil AO, Lee WM; Acute Liver Failure Study Group. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005 Dec;42(6):1364-72
3. Department of Veterans Affairs Office of Inspector General. Healthcare Inspection – VA Patterns of Dispensing Take-Home opioids and Monitoring Patients on Opioid Therapy (Report No. 14-00895-163). May 14, 2014. Washington, DC. Available at: <http://www.va.gov/oig/pubs/VAOIG-14-00895-163.pdf> . Accessed May 16, 2014.
4. Bower WA, Johns M, Margolis HS, Williams IT, Bell BP. Population-based surveillance for acute liver failure. *Am J Gastroenterol*. 2007 Nov;102(11):2459-63. Epub 2007 Jun 29. Erratum in: *Am J Gastroenterol*. 2008 Jan;103(1):255
5. Food and Drug Administration. Prescription Drug Products Containing Acetaminophen: Actions to Reduce Liver Injury from Unintentional Overdose. Available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0021-0001> . Accessed 2014 May 19.
6. FDA for Consumers: New Steps Aimed at Cutting Risks from Acetaminophen. 1-13-2011. Available at: <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm239747.htm> .
7. FDA News Release. FDA limits acetaminophen in prescription combination products; requires liver toxicity warnings. 1-13-2011. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm239894.htm> .
8. Acetaminophen – Acute. *POISINDEX® System* [intranet database]. Version 2.0. 2014. Greenwood Village, CO: Truven Health Analytics, Micromedex.
9. FDA recommends health care professionals discontinue prescribing and dispensing prescription combination drug products with more than 325 mg of acetaminophen to protect consumers. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm381644.htm> . 1-14-2014.
10. FDA reminds health care professionals to stop dispensing prescription combination drug products with more than 325 mg of acetaminophen. 4-28-2014. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm394916.htm> .
11. FDA Drug Safety and Availability: All manufacturers of prescription combination drug products with more than 325 mg of acetaminophen have discontinued marketing. 3-26-2014. Available at: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm390509.htm> .
12. FDA Drug Safety and Availability. Questions and Answers about Oral Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit. 1-13-2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm239871.htm> .

ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives**: Forward this document to all appropriate providers and health care staff (e.g., **primary care providers, pain management staff, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D**: Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).