



DEVAL L. PATRICK
Governor

*The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Office of Medicaid
100 Hancock Street, 6th Floor
Quincy, MA 02171*



JOHN W. POLANOWICZ
Secretary

KRISTIN THORN
Medicaid Director

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Subject: Prior authorization for codeine use in members under 10 years of age

Key points:

- Medical literature and FDA warnings suggest risk of opioid toxicity with codeine use in some children.
- Metabolism of codeine to morphine is highly variable; outcomes may range from ineffective analgesia to toxicity.
- Prescribers may want to consider avoiding the use of codeine for pediatric pain.
- Effective with the November/December 2014 MassHealth Drug List update, MassHealth will require prior authorization for products containing codeine prescribed to members under 10 years of age.

Dear Prescriber,

This letter is a follow-up to a notification sent in August 2013 regarding pediatric codeine use, which warned prescribers of the potential dangers associated with the use of codeine in children. As you may know, the medical literature has reported cases of respiratory depression and death in pediatric patients who were administered codeine within recommended dosing ranges after undergoing tonsillectomy and/or adenoidectomy for treatment of obstructive sleep apnea (OSA).^{1,2} In August 2012, the Food and Drug Administration (FDA) issued a safety announcement which was later strengthened in February 2013 after 13 cases of pediatric death (N=10) or opioid overdose (N=3) had been reported through 2012 in children ages 21 months to nine years. Most of these deaths were in the setting of adenotonsillectomy or respiratory infection, and the announcement indicated that codeine should not be used for pain in children following tonsillectomy and/or adenoidectomy, and resulted in the addition of a Boxed Warning to drug labels of codeine-containing products.³ The updated FDA announcement also states that codeine should be used in other types of pediatric pain only if the benefits outweigh the risks, and should be used only on an as-needed basis.³

Codeine metabolism can be unpredictable and potentially dangerous in patients considered ultra-rapid CYP2D6 metabolizers, including up to 29% of patients of certain ethnic backgrounds and approximately 1% to 7% of the general population.³ Ultra-rapid CYP2D6 metabolism may enhance the conversion of codeine to morphine at a rate that may lead to unanticipated, and sometimes life-threatening opiate overdoses, especially in young children.⁴ Conversely, the percentage of patients considered poor CYP2D6 metabolizers can range from approximately 1% to 30%, depending on ethnic group, and there is little to no analgesic effect from codeine in these individuals.^{2,5} In addition to these concerns, there is the high rate of side effects associated with codeine use and a lack of clinical trials demonstrating its efficacy for treatment of pain and for use as an antitussive.⁶

Several organizations and professional societies have discouraged the use of codeine in children, including the World Health Organization (WHO) and the American Academy of Pediatrics.⁷ However, these warnings have not always been heeded. For example, a study by Kaiser, et. al. evaluated national trends in the prescribing of codeine in children.⁸ This study found that between 2001 and 2010, the proportion of emergency department visits in the U.S. for patients ages 3 to 17 years that resulted in codeine prescriptions showed a statistically significant decrease from 3.7% to 2.9%; however, there was no statistically significant decrease in the

frequency of codeine prescriptions specifically for injury visits (1.8% to 1.6%, $P=0.72$), or upper respiratory infection/cough visits (0.5% to 0.4%, $P=0.28$), or in opioid prescriptions for all visits (8.5% to 10.5%, $P=0.06$).⁷ The authors also compared codeine prescribing since the 2006 issuance of warnings against codeine use for cough and/or upper respiratory infection from the American Academy of Pediatrics and American College of Chest Physicians, and found that there was no statistically significant change.⁸

Given the above referenced safety and efficacy concerns, effective with the November/December 2014 MassHealth Drug List update, MassHealth will require prior authorization for products containing codeine prescribed to members under 10 years of age.

MassHealth encourages prescribers to carefully consider the risks of codeine when evaluating analgesic options for their pediatric patients. Acetaminophen and ibuprofen have shown analgesic efficacy comparable or superior to codeine in acute pain situations.⁹⁻¹¹ If opioid use is required, options such as morphine or oxycodone may represent alternatives with more reliable metabolism than codeine, which has properties that may make prediction of both safety and efficacy more difficult. If CYP2D6 genotyping has been performed, that information must be submitted with any prior authorization request for codeine.

We appreciate your continued support and dedication to providing care to MassHealth members. The MassHealth Drug List, including Therapeutic Class Table 8 outlining the coverage status of codeine and other opioids, can be found on the MassHealth Pharmacy website at www.mass.gov/masshealth/pharmacy.

Sincerely,



Paul L. Jeffrey, PharmD
Pharmacy Director
MassHealth

¹ Ciszkowski C, Madadi P. Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Eng J Med*. 2009 Aug;361(8):827-828.

² Kelly LE, Rider M, van den Anker J, Malkin B, Ross C, Neely MN, et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics*. 2012 Apr;129(5):e1343-7.

³ FDA safety communication: Safety review update of codeine use in children: new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy [press release on the Internet]. Rockville (MD): Food and Drug Administration (US); 2013 Feb 20 [cited 2013 Jul 25]. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm>.

⁴ Kirchheiner J, Schmidt H, Tzvetkov M, Keulen JT, Lotsch J, Roots I, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J*. 2007 Aug;7(4):257-65.

⁵ World Health Organization (WHO). WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses [guideline on the internet]. Geneva, Switzerland: World Health Organization; 2012 [cited 2013 Jul 25]. Available from: http://whqlibdoc.who.int/publications/2012/9789241548120_Guidelines.pdf

⁶ Woolf AD, Greco C. Why can't we retire codeine? *Pediatrics*. 2014 May; 133(5): e1354-5.

⁷ World Health Organization (WHO). WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses [guideline on the internet]. Geneva, Switzerland: World Health Organization; 2012 [cited 2013 Jul 25]. Available from: http://whqlibdoc.who.int/publications/2012/9789241548120_Guidelines.pdf

⁸ Kaiser SV, Asteria-Penalzoza R, Vittinghof E, Rosenbluth G, Cabana MD, Bardach NS. National patterns of codeine prescriptions for children in the emergency department. *Pediatrics*. 2014 May; 133(5): e1128-38.

⁹ Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics*. 2007 Mar;119(3):460-7.

¹⁰ Drendel AL, Gorelick MH, Weisman SJ, Lyon R, Brousseau DC, Kim MK. A randomized clinical trial of ibuprofen versus acetaminophen with codeine for acute pediatric arm fracture pain. *Ann Emerg Med*. 2009 Oct;54(5):553-60.

¹¹ Moir MS, Bair E, Shinnick P, Messner A. Acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy. *Laryngoscope*. 2000 Nov;110(11):1824-7.