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Prior Authorization Review: Codeine

Background:
During the May Pharmacy and Therapeutics (P&T) Committee meeting, the Committee voted to establish Prior Authorization (PA) for use of codeine in children. A safety review of codeine was therefore conducted to determine appropriate criteria for safe use.

Codeine is commonly used to manage moderate pain and reduce cough, but has its limitations as an unpredictable analgesic. Codeine is a prodrug that requires conversion into morphine by cytochrome P450 2D6 (CYP2D6), but its conversion is subject to wide genetic variation leading to either poor pain control in some patients, or at the opposite spectrum, high risk for morphine overdose in others. Codeine is available as a single-ingredient product or in combination with acetaminophen or aspirin and in some cough and cold medications. During 2011, 1.7 million pediatric patients (0-17 years of age) received a prescription for a codeine product from U.S. outpatient retail pharmacies.[1] Interestingly, prescriptions for codeine-containing products only slightly decreased in frequency between 2001 and 2010, despite convincing studies documenting their lack of benefit and serious adverse effects.[2] Indeed, claims for codeine products are commonly encountered for pediatric patients covered under the Oregon Health Plan (OHP).

Fifteen deaths (n=12) or overdoses (n=3) of children (ages 21 months to 12 years) who received standard doses of codeine have been reported in the U.S.[1,3] Many of these children had obstructive sleep apnea and received codeine post-operatively after tonsillectomy and/or adenoidectomy.[1,3] Children who died were found to have very elevated levels of morphine in their blood, which likely further compromised their respiratory function after these particular surgeries.[1,3] Most of these children were also found to have an inherited genetic variant of CYP2D6, the enzyme that metabolizes codeine to morphine.[1,3] Patients with this enzyme variant very rapidly metabolize codeine, resulting in increased risk of developing life-threatening or fatal amounts of morphine in the body. These patients are considered "ultra-rapid metabolizers" of CYP2D6. Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine.[1]

The prevalence of the ultra-rapid CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not currently available for other ethnic groups.[1]

The U.S. Food and Drug Administration (FDA) issued its strongest warning (Boxed Warning) of risk for respiratory failure and death in children who are ultra-rapid metabolizers of codeine due to the CYP2D6 variant.[4] However, routine CYP2D6 genotype testing is not recommended because patients with normal metabolism may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers.[1] Therefore, the FDA issued a Contraindication, which is a formal means for the FDA to make a strong recommendation against use of a drug in certain patients, to restrict any codeine product from being used for post-operative pain in any child who has undergone tonsillectomy and/or adenoidectomy.[4] For management of other types of pain in children, the FDA advises codeine should only be used if the benefits are anticipated to outweigh the risks.[4]

The European Medicines Agency,[5] the United Kingdom's Medicines and Healthcare Products Regulatory Agency,[6] and Health Canada[7] have also issued warnings regarding use of codeine in pediatric patients; but these agencies also provide guidance for use of codeine in children. Briefly, these agencies advise to restrict codeine use for acute moderate pain only (not cough) in children older than 12 years of age, and only if pain is not relieved by acetaminophen or ibuprofen.[5-7] Similar to FDA labeling, these agencies also state codeine is contraindicated in all children younger than 18 years who undergone tonsillectomy or adenoidectomy (or both) for obstructive sleep apnea.[5-7] In children aged 12-17 years, codeine should not be prescribed for more than 3 days at a maximum daily dose of 240 mg.[5]

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Recommendations:

- Promote safe use of codeine and codeine-containing products through Prior Authorization criteria that prohibit use in patients less than 13 years of age and restrict use in patients 13-17 years of age (see **Appendix 1**).
- Perform drug use reviews and provide appropriate prescriber education.

References:

1. FDA Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy [2-20-13]. U.S. Food and Drug Administration. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm . Accessed 9 June 2015.

2. Racoosin JA. Death and respiratory arrest related to ultra-rapid metabolism of codeine to morphine. U.S. Food and Drug Administration, FDA Advisory Committee presentation. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm343601.pdf . Accessed 9 June 2015.

3. Kaiser S, Asteria-Penaloza R, Vittinghoff E, et a.. National patterns of codeine prescriptions for children in the emergency department. Pediatrics. Pediatrics. 2014;133:e1139-e1147. doi:10.1542/peds.2013-3171.

4. Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER). U.S. Food and Drug Administration. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm356221.htm . Accessed 9 June 2015.

5. Pharmacovigilance Risk Assessment Committee recommends restricting use of codeine when used for pain relief of children [6-14-13]. The European Medicines Agency. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001813.jsp&mid=WC0b01ac058004d5c1 . Accessed 9 June 2015.

6. Drug Safety Update: Codeine for analgesia: restricted use in children because of reports of morphine toxicity [7-10-13]. Medicines and Healthcare Products Regulatory Agency, United Kingdom. https://www.gov.uk/drug-safety-update/codeine-for-analgesia-restricted-use-in-children-because-of-reports-of-morphine-toxicity . Accessed 9 June 2015.

7. Health Canada's review recommends codeine only be used in patients aged 12 and over. Health Canada. Availabe at: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php . Accessed 9 June 2015.

Codeine

Goal(s):

- Promote safe use of codeine

Length of Authorization:

Up to 3 days

Requires PA:

- All patients under 18 years of age
- All drug products containing codeine

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. What is the age of the patient?	Ages 0-12 years: Pass to RPh. Deny; medical appropriateness	Ages 13-17 years: Go to #3
3. Is the prescription for an OHP-funded condition?	Yes: Pass to RPh. Deny; not funded by the OHP	No: Go to #4
4. Has the patient recently undergone tonsillectomy or adenoidectomy?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #5
5. Does the dose exceed 240 mg per day?	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve no more than 3-day supply

P&T / DUR Review: *7/15 (AG)*
Implementation: *TBD*