Codeine and tramadol – New contraindications and warnings

- On April 20, 2017, the FDA announced that new updates will be made to the *Contraindications* and *Warnings* sections of all prescription codeine and tramadol drug products regarding their use in children, adolescents and breastfeeding women.

- Codeine is an opioid used to treat mild to moderate pain and also to reduce coughing. Single ingredient codeine is approved for pain management in adults only.

- Codeine is usually combined with other medicines [eg,Tylenol® with codeine (acetaminophen/codeine)] in prescription pain products. It is frequently combined with other drugs in prescription and over-the-counter (OTC) cough and cold medicines [eg, Cheratussin® AC (codeine/guaifenesin), promethazine/codeine].

- Tramadol is a prescription opioid drug approved only for use in adults to treat moderate to moderately severe pain. Tramadol is available as single ingredient (Ultram®, Ultram® ER, and ConZip®) and combination [Ultracet® (tramadol/acetaminophen)] products.

- The FDA is adding the following to all prescription codeine and/or tramadol products:

    — A contraindication to codeine and tramadol drug labels stating that these products should not be used in children < 12 years of age.

    — A contraindication to the tramadol drug label warning against its use in children < 18 years of age to treat pain after surgery to remove the tonsils and/or adenoids.

    — A new warning to codeine and tramadol drug labels recommending against their use in adolescents between 12 and 18 years of age who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.

    — A strengthened warning stating that breastfeeding is not recommended when taking codeine or tramadol due to the risk of serious adverse reactions in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death.

- *FDA recommendations for healthcare providers:*

    — All tramadol-containing products and single-ingredient codeine drugs are FDA-approved for use only in adults.

    — Other OTC or FDA-approved prescription medicines should be considered for cough and pain management in children and adolescents < 18 years of age, especially those with certain genetic factors, obesity, or obstructive sleep apnea and other breathing problems. Cough is often secondary to infection and will typically resolve on its own.

    — If a codeine- or tramadol-containing product is appropriate for an adolescent patient, parents and caregivers should be counseled on how to recognize the signs of opioid toxicity, and advised to stop giving the adolescent codeine or tramadol and seek medical attention immediately if their adolescent is exhibiting these signs.

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- If patients of any age are known to be CYP2D6 ultra-rapid metabolizers, which means their bodies convert codeine or tramadol into their active forms faster and more completely than usual, they should not use codeine or tramadol.

- *FDA recommendations for caregivers and patients:*

  - The caregiver/patient should always read the label on prescription bottles or ask a healthcare provider to find out if a medicine contains codeine or tramadol. Caregivers should monitor for signs of breathing problems in a child of any age who is taking these medicines or in infants exposed to codeine or tramadol through breast milk.

    - Signs of breathing problems include slow or shallow breathing, difficulty or noisy breathing, confusion, more than usual sleepiness, trouble breastfeeding, or limpness.
    - If any of these symptoms occur, the medicine should not be used and the caregiver/patient should seek medical attention immediately.

- The safety update is based on information from adverse event reports of respiratory depression, including some deaths, of children administered codeine or tramadol. Some cases involved patients identified as ultra-rapid metabolizers. A review of the medical literature for data regarding codeine use during breastfeeding found numerous case reports of respiratory depression and sedation, including one death, of breastfed infants.

- In 2013, the FDA added a boxed warning to the codeine drug label cautioning against prescribing codeine to children of any age to treat pain after surgery to remove tonsils or adenoids. In 2015, the FDA also issued drug safety communications warning about the risk of serious breathing problems in children identified as CYP2D6 ultra-rapid metabolizers. An FDA Advisory Committee meeting was also held to discuss these codeine-related safety issues.

- The FDA will continue to monitor these safety issues and is considering additional regulatory action for the OTC codeine products that are available in some states. The FDA is also considering an FDA Advisory Committee meeting to discuss the role of prescription opioid cough-and-cold medicines, including codeine, to treat cough in children.