U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women

This is an update to the FDA Drug Safety Communications:

- FDA evaluating the potential risks of using codeine cough-and-cold medicines in children issued on July 1, 2015, and
- FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger issued on September 21, 2015.

Safety Announcement

[4-20-2017] The Food and Drug Administration (FDA) is restricting the use of codeine and tramadol medicines in children. Codeine is approved to treat pain and cough, and tramadol is approved to treat pain. These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults. We are also recommending against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.

As a result, we are requiring several changes to the labels of all prescription medicines containing these drugs. These new actions further limit the use of these medicines beyond our 2013 restriction of codeine use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids. We are now adding:

- FDA's strongest warning, called a *Contraindication*, to the drug labels of codeine and tramadol alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years.
- A new *Contraindication* to the tramadol label warning against its use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years 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* to mothers that breastfeeding is not recommended when taking codeine or tramadol medicines 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.

Caregivers and patients should always read the label on prescription bottles to find out if a medicine contains codeine or tramadol. You can also ask your child's health care provider or a pharmacist. Watch closely 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 breastmilk. These signs include slow or shallow breathing, difficulty or noisy breathing, confusion, more than usual sleepiness, trouble breastfeeding, or limpness. If you notice any of these signs, stop giving the medicine and seek medical attention immediately by going to an emergency room or calling 911.

Health care professionals should be aware that tramadol and single-ingredient codeine medicines are FDA-approved only for use in adults. Consider recommending over-the-counter (OTC) or other FDA-approved prescription medicines for cough and pain management in children younger than 12 years and in adolescents younger than 18 years, especially those with certain genetic factors, obesity, or obstructive sleep apnea and other breathing problems. Cough is often secondary to infection, not serious, and usually will get better on its own so treatment may not be necessary.

Codeine and tramadol are a type of narcotic medicine called an opioid. Codeine is used to treat mild to moderate pain and also to reduce coughing. It is usually combined with other medicines, such as acetaminophen, in prescription pain medicines. It is frequently combined with other drugs in prescription and over-the-counter (OTC) cough and cold medicines. Tramadol is a prescription medicine approved only for use in adults to treat moderate to moderately severe pain. However, data show it is being used in children and adolescents despite the fact that it is not approved for use in these patients.

In early 2013, 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. We also issued Drug Safety Communications in July 2015 and September 2015 warning about the risk of serious breathing problems in some children who metabolized codeine and tramadol much faster to their active form than usual (called ultra-rapid metabolism), causing potentially dangerously high levels in their bodies too quickly. At that time, we said we would continue to evaluate this safety issue. As part of that safety review, the codeine-related safety issues were discussed at an FDA Advisory Committee meeting in December 2015.

Our review of several decades of adverse event reports submitted to FDA* from January 1969 to May 2015 identified 64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years. This includes only reports submitted to FDA, so there may be additional cases about which we are unaware. We also identified nine cases of serious breathing problems, including three deaths, with the use of tramadol in children younger than 18 years from January 1969 to March 2016 (see Data Summary). The majority of serious side effects with both codeine and tramadol

occurred in children younger than 12 years, and some cases occurred after a single dose of the medicine.

In our review of the medical literature[1-19] for data regarding codeine use during breastfeeding, we found numerous cases of excess sleepiness and serious breathing problems in breastfed infants, including one death. A review of the available medical literature[4,5,23,24] for data regarding tramadol use during breastfeeding did not reveal any cases of adverse events. However, tramadol and its active form are also present in breast milk, and tramadol has the same risks associated with ultra-rapid metabolism as codeine.

We will continue to monitor this safety issue. We are considering additional regulatory action for the OTC codeine products that are available in some states. OTC codeine products are available in combination with other medicines for cough and cold symptoms. We are 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.

We urge patients and health care professionals to report side effects involving codeine- and tramadol- containing medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS).

List of Prescription Codeine and Tramadol Pain and Cough Medicines

Medicines Containing Codeine	Medicines Containing Tramadol
Codeine Sulfate	Conzip
Butalbital, Acetaminopen, Caffeine, and Codeine phosphate	Ultracet
Fiorinal with codeine	Ultram
Soma Compound with codeine	Ultram ER
Tylenol with codeine	Generic products containing tramadol
Promethazine with codeine (cough)	
Prometh VC with codeine (cough)	
Triacin-C (cough)	
Tuxarin ER (cough)	
Tuzistra-XR (cough)	
Generic products containing codeine	
Medicines Containing Dihydrocodeine	
Synalgos-DC	

Facts about Codeine and Tramadol

- Codeine

- An opioid pain reliever used to treat mild to moderate pain. It is usually combined with other medicines, such as acetaminophen, in prescription pain medicines.
- Single-ingredient codeine is approved for pain management in adults only.
- Also used to reduce coughing. It is frequently combined with promethazine in prescription cough-and-cold medicines and with other cold remedies in over-the-counter (OTC) preparations.
- Common side effects include drowsiness, lightheadedness, dizziness, feeling tired, shortness of breath, nausea, vomiting, stomach pain, constipation, itching, or rash.
- In 2014, nearly 1.9 million patients 18 years of age and younger received a dispensed prescription for codeine-containing products from U.S. outpatient retail pharmacies. Of the total pediatric patients, nearly 1.4 million patients received codeine-containing analgesic products, and 483,000 patients received codeine-containing cough-and-cold products.[20]

- Tramadol
  - An opioid pain reliever FDA-approved only in adults to treat moderate to moderately severe pain.
  - Available as a single ingredient under the brand names Ultram, Ultram ER, Conzip and also as generics.
  - Also available in combination with acetaminophen under the brand name Ultracet and as generics.
  - Common side effects include headache, dizziness, drowsiness, feeling tired, constipation, diarrhea, nausea, vomiting, stomach pain, itching, or flushing.
  - In 2014, nearly 167,000 patients younger than 18 years of age received a dispensed prescription for tramadol-containing products from U.S. outpatient retail pharmacies. [21]

Additional Information for Caregivers and Patients

- FDA is warning about several safety issues with prescription medicines containing codeine used for pain or cough and tramadol used for pain:
  - Codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years due to the risk of serious side effects, including slowed or difficult breathing and death.
  - Codeine is not recommended to treat cough or pain and tramadol is not recommended to treat pain in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease that may increase the risk of breathing problems.
  - Tramadol should not be used to treat pain in children up to 18 years of age after surgery to remove their tonsils and/or adenoids. The drug label for codeine already warns against use in children up to 18 years of age after surgery to remove their tonsils and/or adenoids.

    - Breastfeeding is not recommended during treatment with codeine or tramadol because the medicine passes through breast milk and can harm the baby.
- Talk to your health care provider or a pharmacist to find out if a medicine your child is taking contains codeine or tramadol.
- Always read the label on prescription bottles to find out if a medicine contains codeine or tramadol, or ask your child's health care provider or a pharmacist.
- 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.
- If a child has taken codeine or tramadol and you notice any signs of slow or shallow breathing, difficult or noisy breathing, confusion, or unusual sleepiness in a child of any age, seek medical attention immediately by taking the child to an emergency room or calling 911.
- Report any side effects from codeine- or tramadol- containing medicines to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA is warning about several safety issues with prescription medicines containing codeine used for pain or cough and tramadol used for pain and requiring the following changes to the drug labels:
    - FDA's strongest warning, called a *Contraindication*, alerting that codeine and tramadol should not be used to treat pain in children younger than 12 years, and codeine should not be used to relieve cough in these children.
    - A new *Contraindication* to the tramadol label to restrict its use in children younger than 18 years to treat pain after a tonsillectomy and/or adenoidectomy. The label of codeine-containing products already carry this Contraindication.
    - A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or compromised respiratory function, that may increase the risk of serious breathing problems.
    - Strengthening the *Warning* to patients that breastfeeding is not recommended during treatment with codeine or tramadol due to the potential for serious adverse reactions in a breastfed infant, such as excess sedation, respiratory depression, and death.
- All tramadol-containing products and single-ingredient codeine drugs are FDA-approved for use only in adults.
- If you have determined that a codeine-or tramadol-containing product is appropriate for an adolescent patient, counsel parents and caregivers on how to recognize the signs of opioid toxicity, and advise them to stop giving the adolescent codeine or tramadol and seek medical attention immediately if their adolescent is exhibiting these signs.

- Report adverse events involving codeine- or tramadol- containing medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

Codeine

A search of the FDA Adverse Event Reporting System (FAERS) database from January 1969 to May 2015 identified 64 worldwide cases of respiratory depression, including 24 deaths, with codeine-containing medicines in children younger than 18 years. Fifty cases were reported in children younger than 12 years. Respiratory depression occurred after the children received a range of one to 18 doses, with a median of five doses. The most frequently reported codeine-containing medicines in the cases were acetaminophen with codeine used for pain, and promethazine with codeine (with or without phenylephrine) used for cough and cold.

Of the 24 cases reporting death, 21 occurred in children younger than 12 years. The reasons for codeine-containing medicine use in these cases included post-tonsillectomy and/or adenoidectomy pain management, other post-operative pain, general pain, sore or strep throat pain, and cough and cold.

Ten of the 64 cases mentioned the status of cytochrome P450 isoenzyme 2D6 (CYP2D6) genotype. Seven of these patients were ultra-rapid metabolizers, five of whom died. Ultra-rapid metabolizers of substrates of CYP2D6 convert codeine in their bodies too quickly into potentially dangerously high levels of morphine, the active form of codeine, contributing to life-threatening or fatal respiratory depression. The three other patients were extensive metabolizers, with one death.

Fifteen of the 64 cases reported codeine or morphine blood levels; the remaining 49 cases did not. In 13 cases, the blood levels were above the therapeutic range, and in two cases the blood levels were within the therapeutic range. One patient who had blood levels in the therapeutic range died following pain management post-tonsillectomy and adenoidectomy.

Tramadol

A search of the FAERS database from January 1969 to March 2016 identified nine cases worldwide of respiratory depression in children younger than 18 years of age, including three deaths. With the exception of a 15-year-old treated for multiple days with tramadol, respiratory depression occurred within the first 24 hours of drug administration.

The three fatalities occurred outside the U.S. in children younger than 6 years. Elevated serum tramadol concentrations were noted in all three. The reasons for tramadol treatment in these children were to treat pain after tonsillectomy, pain after clubfoot surgery, and to manage fever. All three cases involved tramadol oral drops, a formulation not available in the U.S.

The one case in which CYP2D6 ultra-rapid metabolizer status was reported occurred in a 5-year-old child from France who was prescribed a single tramadol dose in the evening post-adenotonsillectomy and returned to the healthcare facility the next morning with opioid intoxication; he was resuscitated.[22] A urine sample showed increased metabolite concentrations. Genotyping of CYP2D6 was conducted, and three functional alleles were found that were consistent with ultra-rapid metabolism.

One non-fatal U.S. case involved a 6-year-old who was prescribed tramadol for neuropathy of the hands and feet. After the third dose, the patient experienced respiratory depression and was unresponsive. The patient fully recovered after receiving two doses of naloxone.

Four other non-fatal cases reported in teenagers using tramadol for musculoskeletal pain or sciatica described unresponsiveness or somnolence after one or a few doses of tramadol; all required medical intervention. Two of these were U.S. cases.

Breastfeeding Mothers

Codeine and its active metabolite, morphine, are present in breast milk. A search of the medical literature[1-19] for relevant data regarding codeine use during lactation revealed numerous reports of respiratory depression and sedation, including one infant death, especially in mothers who have the CYP2D6 ultra-rapid metabolizer genotype.

In the case of the infant death, the mother was found to be a CYP2D6 ultra-rapid metabolizer, which potentially led to higher levels of morphine secreted into the breast milk leading to the infant's death. In other studies comparing drowsiness in breastfed babies whose mothers took codeine/acetaminophen compared to acetaminophen alone, the frequency of somnolence was higher in the codeine/acetaminophen-exposed group. Some of the mothers of those babies were CYP2D6 ultra-rapid metabolizers.[15,16]

Mothers who are ultra-rapid metabolizers of codeine achieve higher-than-expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous to their breastfed infants. In women with normal codeine metabolism, the amount of codeine secreted into breast milk is low and dose-dependent.

According to *Drugs in Pregnancy and Lactation*[5], both tramadol and its pharmacologic active metabolite (O-desmethyltramadol) are excreted into human milk. The mean absolute bioavailability of a 100-mg dose is 75%. Thus, ingestion of the recommended dose may produce drug amounts in breast milk that could exceed those reported above. The effect of this exposure on a nursing infant is unknown.

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Related Information

FDA statement from Douglas Throckmorton, M.D., Deputy Center Director for Regulatory Programs, Center for Drug Evaluation and Research, on new warnings about the use of codeine and tramadol in children & nursing mothers

Consumer Update: Codeine and Tramadol Can Cause Breathing Problems for Children

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Tramadol Information

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