

Frequently Asked Questions

Codeine and all multiple-ingredient products containing codeine are restricted on the AHS Provincial Drug Formulary to patients 18 years of age and older.

1. What does this mean?

A restricted formulary drug is one that has specific criteria, limiting how it is prescribed. Compliance to a formulary restriction is required by all Alberta Health Services (AHS) clinicians. Use of drugs outside of a formulary restriction is considered non-formulary use. Restricted drugs are denoted with an “R” in their formulary status code. In AHS, codeine may be ordered without restriction for patients 18 years of age or older. Infants, children and adolescents should not be prescribed codeine and alternative analgesic drugs should be prescribed for this age group.

Should an order for codeine be written for a child in an AHS facility, pharmacists will contact the prescriber to discuss a formulary alternative. Since codeine is a ‘prodrug’ – metabolized to morphine (which is the active form) in the body – morphine is the suggested alternative to codeine, when pain cannot be managed with acetaminophen and ibuprofen alone.

After discussing codeine alternatives with a pharmacist, if a prescriber insists on continuing with the codeine order they should be advised that delays in getting the drug to the patient may occur as the drug may no longer be stocked in the pediatric treatment area.

2. Why is codeine now restricted in this age group?

Codeine is being restricted in pediatrics due to a number of case reports of death and significant adverse effects in children who have a specific genetic polymorphism. These ‘ultra-rapid’ metabolizers have enhanced conversion of codeine to morphine, producing toxic morphine concentrations despite therapeutic codeine doses. Distribution of this genetic polymorphism varies by geographic region with as many as 40% of the population in northern Africa being classified as ultra-rapid metabolizers. It is estimated that approximately 8% of Canadians carry this specific polymorphism. Testing for the genetic variant is not yet available at the bedside and it is impossible to predict who may

be affected, based on the patient's or their family's medication history. To add to the uncertainty, approximately 10% of Canadians are classed as 'poor metabolizers' and are unable to convert codeine to morphine. These people receive very little (if any) benefit from codeine.

For these reasons, codeine is a very poor analgesic choice, as the benefit from codeine depends entirely on the genetic variant of the CYP2D6 gene (CYP2D6 is the enzyme that converts codeine to the active form of morphine).

3. Why doesn't the restriction apply to adult patients?

All age groups would similarly be impacted by the various gene polymorphisms. Adult patients often have the 'benefit' of a longer medication history and prescribers are able to assure themselves that codeine has been safely used by a patient in the past. Adults are also perhaps better able to articulate the sensation of excessive sedation, drowsiness and shallow breathing that may precede an occurrence of respiratory depression. The restriction will only apply to pediatrics at this time.

Obstructive sleep apnea (OSA) is also a recognized risk factor. Many of the pediatric cases reported in the literature involved children who received codeine post-operatively, after tonsillectomy/adenoidectomy surgery for OSA. Patients with underlying OSA should be monitored for respiratory depression regardless of what narcotic they are prescribed.

4. Does this restriction apply to all codeine-containing products, including Tylenol #3?

This restriction applies to all codeine oral products (single-entity products and multi-ingredient preparations) as well as injectable codeine. The full list of products impacted by this restriction is provided below.

Generic Name	Brand Name & Synonyms	Strength	Dosage Form (Size)
acetaminophen-caffeine-codeine phosphate	Tylenol with Codeine No.2, Ratio-Lenoltec No.2, Atasol-15	300mg – 15mg – 15mg	Tablet
acetaminophen-caffeine-codeine phosphate	Tylenol with Codeine No.3, Ratio-Lenoltec No.3, Atasol-15	300mg – 15mg – 30mg	Tablet
acetaminophen-caffeine-codeine phosphate	Tylenol No.1, Ratio-Lenoltec No.1, Atasol-8	300mg – 15mg – 8mg	Tablet
acetaminophen-caffeine-codeine phosphate	Tylenol with Codeine No.4, Ratio-Lenoltec No.4	300mg – 60mg	Tablet
acetaminophen-caffeine-codeine phosphate	Tylenol with Codeine Elixir	32mg – 1.6mg/mL	Elixir
codeine monohydrate – codeine sulfate trihydrate	Codeine Contin	100mg	Tablet, extended release
codeine monohydrate – codeine sulfate trihydrate	Codeine Contin	50mg	Tablet, extended release
codeine phosphate		15mg	Tablet
codeine phosphate		30mg	Tablet
codeine phosphate		5 mg/mL	Syrup
codeine phosphate		30mg/mL	Injection (1mL)

5. What alternatives are available to use in pediatrics?

Pain should be managed in a step-wise approach. Minor discomfort can often be managed by use of ibuprofen alone. Acetaminophen can be added, providing there are no contraindications. For moderate to severe pain it is best to add an opioid early on, rather than let the pain continue. Morphine is the suggested alternative to codeine and is available as a liquid suspension or as immediate release tablets (e.g. 5 mg, 10 mg). Doses should be titrated to effect. A triplicate prescription form must be used when morphine is prescribed for discharge or outpatient use.

a) Acetaminophen

Age	ORAL Acetaminophen Dose	RECTAL Acetaminophen Dose	Maximum Daily Dose
Newborn infants ≤ 38 weeks gestational age	<i>Standard guideline does not apply to this age group.</i>		
Newborn infants > 38 weeks gestational age – infants < 3 months of age	10 – 15 mg/kg/dose po q4-6 h prn	15 - 20 mg/kg/dose pr q8h prn	60 mg/kg/day
Infants ≥ 3 months, children & adolescents up to 18 yrs	10 – 15 mg/kg/dose po q4-6 h prn	20 mg/kg/dose pr q6h prn	Oral: 75 mg/kg/day ^a (or 4 g/day whichever is less) Rectal: 80 mg/kg/day (or 4 g/day whichever is less)

The prescribed dose and dose schedule should be individualized in all patients with appropriate reassessment on a regular ongoing basis. Patients who have one or more of the following risk factors may be more susceptible to hepatotoxicity:

- Children less than 2 years of age

- Fasting or acutely malnourished and/or dehydrated due to vomiting, diarrhea or fever (reduced hepatic glutathione stores)
- Chronic malnutrition
- Viral infection
- Underlying metabolic disease
- Receiving concomitant drugs that induce hepatic cytochrome P450 enzyme function (e.g. phenobarbital, phenytoin, dexamethasone, rifampin, and isoniazid).

^a Children with severe pain may require higher doses. Doses up to a maximum of 90 mg/kg/day (4 g/day) can be given to these patients but only if risk factors are absent. Duration at this dose should be limited to 2-3 days with careful monitoring. Doses should not exceed 90 mg/kg/day (4000 mg day; 4 g/day) under any circumstance. Severe renal impairment requires dosage adjustment.

b) Ibuprofen

Infants & children: 5 – 10 mg/kg/dose every 6-8 hours (Maximum 40 mg/kg/day or 2400 milligrams per day)

c) Morphine

For infants greater than 6 months of age, children and adolescents:

Initial oral dose in opioid naïve: Morphine 0.2 mg/kg/dose (Maximum 10 mg) po q4h prn

- Morphine should be titrated to effect, usually in the dose range of 0.1-0.5mg/kg/dose po q4h prn.
- Dose reduction is required in renal impairment; consult a pediatric dose reference for more information.
- Infants less than 6 months of age require a lower dose; consult a pediatric dose reference for more information.
- Intravenous doses are different than oral doses; consult a pediatric dose reference for more information.

6. What about the use of codeine as an antitussive?

Current evidence finds codeine to be no more effective than placebo for acute cough in children. Due to its safety profile and documented lack of effectiveness codeine is not recommended for the treatment of cough in children.

7. I do not have a Triplicate Prescription pad what can I do?

You can apply for a Triplicate Prescription form at

http://www.cpsa.ab.ca/Services/Triplicate_Prescription_Program/TPP_Overview.aspx

There is no cost to you for these prescription forms.

Triplicate prescriptions should be stored in a secure, locked location. If you do not wish to carry these prescription forms with you, it may be possible to store them in a locked drawer in the patient care area.

Codeine has recently been added to the Triplicate Prescription Program in Alberta as well, but prescriptions for this drug can still be written on a regular prescription pad. While it may be more convenient to write a discharge prescription for codeine, it is preferable to discharge the patient with the same drug they've been using while in hospital.

8. Who was involved in making this decision?

Like all AHS Provincial Drug Formulary decisions, the decision to restrict codeine in pediatrics was carefully contemplated. The Pediatric Advisory Committee (PAC) is a multi-disciplinary committee made up of pediatric practitioners from across the province. The PAC reports to the Drugs and Therapeutics Committee of AHS. Discussions occurred at several of these committee meetings with both committees ultimately agreeing that there was a potential for significant harm from codeine in the pediatric population and as such a restriction on its use in the pediatric population was required.

The Hospital for Sick Children in Toronto and the Children's Hospital of Eastern Ontario, have removed codeine from their respective formularies. Several other North American hospitals have also taken this direction. Health Canada has also issued a warning about use of codeine in children less than 12 years of age.

<http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php>