

Health Canada Endorsed Important Safety Information on  
N<sup>o</sup>TYLENOL\* with Codeine



JANSSEN-ORTHO

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Version Number 01

Dear Health Care Professional:

**Subject: Important Safety Information about use of N<sup>o</sup>TYLENOL\* with Codeine NO 2, 3, 4 and Elixir in Nursing Mothers and Ultra-Rapid metabolizers of Codeine**

Janssen-Ortho Inc. in collaboration with Health Canada would like to highlight new safety information regarding the use of TYLENOL with Codeine NO 2, 3, 4 and Elixir in nursing mothers and ultra-rapid metabolizers of codeine.

- Some individuals may be ultra-rapid metabolizers of codeine due to a specific CYP2D6 genotype.
- Breastfed babies of women who are ultra-rapid metabolizers are potentially at risk of dangerously high serum morphine levels due to higher-than-expected levels of morphine in the mother's breast milk.
- Mothers using codeine should be informed of signs and symptoms of morphine toxicity for themselves (constipation, oversedation) or their babies (drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone).
- Codeine-containing products should be prescribed at the lowest effective dose and for the shortest period of time.

Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people leading to higher-than-expected serum morphine levels. Even at labelled dosage regimens, individuals who are ultra-rapid metabolizers may experience toxicity symptoms such as extreme sleepiness, confusion, or shallow breathing.

The prevalence of the CYP2D6 genotype varies widely among the population and has been estimated to be at 0.5 to 1% in patients of Chinese, Japanese and Hispanic origin, 1 to 10% in patients of Caucasian origin, 3% in patients of African American origin, and 16 to 28% in patients of North African, Ethiopian, and Arab origin (1). Data are not available for other ethnic groups.

When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and inform patients about the risk and signs of morphine toxicity.

Codeine is secreted in human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in infants are rare.

However, women who are ultra-rapid metabolizers achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants. The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine-containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience toxicity symptoms such as extreme sleepiness, confusion, or shallow breathing.

Janssen Ortho Inc. will be updating the Warnings and Precautions section of the Canadian Product Monograph for TYLENOL with Codeine NO 2, 3, 4 and Elixir to include the new important safety information regarding the risk of morphine toxicity in ultra-rapid metabolizer nursing mothers.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious adverse reaction in mother-infant pairs or other serious or unexpected adverse reactions in patients receiving TYLENOL with Codeine should be reported to Janssen-Ortho Inc. or Health Canada at the following addresses:

Janssen-Ortho Inc.  
Drug Safety Department  
19 Green Belt Drive  
Toronto, ON M3C 1L9  
Tel: (800) 567-3331 or Fax: (866) 767-5865  
dsscan@joica.jnj.com

**Any suspected adverse reaction can also be reported to:**

Canada Vigilance Program  
Marketed Health Products Directorate  
HEALTH CANADA  
Address Locator: 0701C  
Ottawa, Ontario, K1A 0K9  
Tel: 613-957-0337 or Fax: 613-957-0335  
To report an Adverse Reaction, consumers and health professionals may call toll free:  
Tel: 866-234-2345  
Fax: 866-678-6789  
[CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

The [AR Reporting Form](#) and the [AR Guidelines](#) can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

[http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei\\_form-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form-eng.php)  
[http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/\\_guide/2008-ar-ei\\_guide-ldir/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2008-ar-ei_guide-ldir/index-eng.php)

**For other inquiries related to this communication, please contact Health Canada at:**

Marketed Health Products Directorate  
E-mail: [mhpd\\_dpssc@hc-sc.gc.ca](mailto:mhpd_dpssc@hc-sc.gc.ca)  
Tel: 613-954-6522  
Fax: 613-952-7738

A copy of this letter can be found at [www.janssen-ortho.com](http://www.janssen-ortho.com), and at <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>.

Sincerely,

**Original signed by**



Cathy Lau, PhD  
Vice President Regulatory and Quality

**References:**

1. Use of Codeine Products in Nursing Mothers - Questions and Answers. Food and Drug Administration. <http://www.fda.gov/cder/drug/infopage/codeine/qa.htm> Posted 2007-08-17. Accessed 2008-09-10.

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