

**Notice Information: Human Medicines - Advisory
28 January 2008**

Part 1. Product Information

a) Title:

b) Product Name/Type:

c) Active Substance:

Part 2. Problem/Issue

a) Problem/Issue:

The IMB would like to alert healthcare professionals and patients to a rare but serious adverse reaction that may occur in babies of nursing mothers who take analgesics containing codeine. Codeine should not be used by breastfeeding mothers, unless prescribed by a physician. Codeine is a weak opioid which may be used for postpartum analgesia e.g. following caesarean section or episiotomy. It is metabolised by O- and N-demethylation in the liver to morphine, norcodeine, and other metabolites which are subsequently excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The cytochrome P450 enzyme (CYP2D6) is required for the conversion of codeine into morphine. Due to genetic variations, between 1-10% of caucasians have markedly increased CYP2D6 activity (although the prevalence is higher in some other racial groups); such individuals are ultrarapid metabolisers and are more likely to experience adverse reactions when given codeine, because they convert codeine to morphine more quickly or in greater quantities. The genetic variation of CYP2D6 may be determined by genotyping. Codeine usually passes into breast milk in clinically insignificant amounts and so most breastfeeding women will be able to take codeine, where medically indicated. However, in the case of breastfeeding mothers who are ultrarapid metabolisers, higher than expected morphine levels in blood and breast milk can occur, with consequential adverse effects on the neonate/infant. A case report in the Lancet described a breastfed neonate who died from morphine toxicity associated with therapeutic use of maternal codeine. In this case, the mother was subsequently identified as an ultra-rapid codeine metaboliser. (Koren G, et al. Lancet 2006; 368: 704.) Codeine should not be used by breastfeeding mothers unless prescribed by a physician. The lowest effective dose should be used for the shortest possible time. If any signs or symptoms of opioid toxicity develop in a breastfeeding mother or infant, all codeine containing medicines should be stopped immediately and alternative analgesics prescribed. In severe cases, use of naloxone to reverse the effects, may be appropriate. To date, the IMB has not received any reports of signs or symptoms of opioid toxicity occurring in breastfeeding mothers or their infants in Ireland. Healthcare professionals should advise breastfeeding mothers about the typical adverse effects of opioids, the need to carefully monitor for any signs and symptoms of maternal opioid toxicity or infant opioid toxicity e.g. somnolence, feeding or breathing difficulties, hypotonia and miosis and to seek immediate medical attention if such signs become apparent. Healthcare professionals are reminded to report any suspected adverse reactions associated with codeine containing products to the IMB in the usual way