CYP2D6: codeine 1583/1584/1585

AUC = area under the concentration-time curve, Cl_{or} = oral clearance, EM = extensive metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), IM = intermediate metaboliser (gene dose 0,5-1) (decreased CYP2D6 enzyme activity), M3G = morphine-3-glucuronide, M6G = morphine-6-glucuronide, MR = metabolic ratio, NS = non-significant, OR = odds ratio, PCA = patient-controlled analgesia, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, UM = ultra-rapid metaboliser (gene dose ≥ 3) (enhanced CYP2D6 enzyme activity)

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Codeine is primarily metabolised by CYP3A4, CYP2D6 and by glucuronidation. Conversion by CYP2D6 results in formation of the active metabolite morphine, which has a 200x higher affinity for the μ-opioid receptor than codeine itself. Morphine is further converted to morphine-3-glucuronide and the active morphine-6-glucuronide. Conversion by CYP3A4 results in formation of the metabolite norcodeine, which does not have a therapeutic activity at the μ-opioid receptor.
The analgesic effect of codeine is caused by the active metabolites morphine and morphine-6-glucuronide.

- For the indication of **pain**, six studies with in total 37 healthy PM showed absent or strongly diminished analgesia with codeine. Diminished analgesia was confirmed in one study with patients (2 PM), but not in 5 patient studies with in total 30 PM. However, in the patient studies, codeine was generally given together with paracetamol or rescue medication was provided. As for PM, diminished formation of morphine was observed for IM. The working group concludes that there is a gene-drug interaction for PM and IM and that adjustment of therapy is required (yes/yes interactions).
  For UM, a study with breast feeding mothers (5 UM) showed that this genotype increased the risk of codeine-induced central nervous system depression in the mother and infant. Another study with 6 UM showed that this could be prevented by maternal use of codeine for maximally 4 days and informing the mothers about adverse events. In one case, an infant of a breastfeeding mother died after maternal codeine use. Another infant became drowsy, but recovered after breastfeeding was stopped. In another study, 2 UMs avoided codeine use due to adverse events, while the only adverse event in the third UM was obstipation. Two children died after using codeine for pain relief after tonsillectomy. Three paediatric UM experienced sedation on postoperative day 1. One adult UM developed codeine-induced severe abdominal pain. According to the label, use of codeine is contra-indicated for UMs. The working group concludes that action is needed for this gene-drug interaction (yes/yes-interaction).
  The recommended therapy adjustments are indicated below.

Both codeine and the metabolite morphine result in suppression of the cough reflex in the cough centre of the *medulla oblongata*. The cough-suppressing effect of codeine is approximately three times stronger than that of morphine (Nattermann: Klinisches sachverständigen-gutachten zu Bronchicum Mono Codein Tropfen, April 2006).

- There is not enough evidence in the literature to warrant a modification of the therapy for the indication of **cough.** No data have been published for research into the effect of the genotype/phenotype with use of codeine for cough. The calculated dose adjustment (based on the AUC of codeine) is a dose reduction to 89% of the standard dose, which is probably not clinically relevant.
  For UM, the only evidence for adverse events at the lower doses used for the indication of cough is one case report of an adult patient with the additional risk factors of co-medication with two CYP3A4 inhibitors and impaired renal function (Gasche 2004). For this reason, the working group decides that an alternative is only required in case of additional risk factors, such as co-medication with CYP3A4 inhibitors and/or impaired renal function.
  The recommended therapy adjustments are indicated below.

You can find a detailed overview of the observed kinetic and clinical effects in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.
The justification for the therapeutic recommendations you will find below.

Therapeutic recommendations

- For the indication of **pain** (doses higher than 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older), it is preferable to select an alternative for PM and UM that is not metabolised by CYP2D6. Do not select tramadol, as this is also metabolised by CYP2D6. Morphine is not metabolised by CYP2D6. Due to the lack of solid evidence for a decrease in efficiency for IM, extra alertness to a reduced effectiveness is recommended first, followed by a dose increase or alternative in case of inadequate effectiveness. It is not possible to offer adequately substantiated advice for dose adjustment based on the literature if codeine is used for analgesia. As the enzyme activity is limiting in PMs and IMs, a dose increase might not be useful here. Be extra alert to a reduced effectiveness if codeine is given to PMs and IMs. Use of codeine is contra-indicated for UMs.
- For the indication of **cough** (maximum doses of 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older), no therapy adjustment is needed for IM and PM. For UM, use of codeine is contra-indicated in case of additional risk factors, such as co-medication with CYP3A4 inhibitors and/or impaired renal function and an alternative should be selected. Noscapine is not metabolised by CYP2D6.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The Dutch Pharmacogenetics Working Group considers genotyping before starting codeine in doses higher than 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older, and in patients with additional risk factors, such as co-medication with CYP3A4 inhibitors and/or impaired renal function, to be beneficial for drug safety. It is advised to genotype these patients before (or directly after) drug therapy has been initiated to guide drug and dose selection.
The clinical implication of the gene-drug interaction scores 4 out of the maximum of 10 points (with pre-emptive genotyping considered to be beneficial for scores ranging from 3 to 5 points):
An ultra-rapid metaboliser with impaired renal function and using two CYP3A4 inhibitors became comatose 4 days after starting codeine 25 mg 3 times daily to combat cough. In addition, cases of fatal adverse events have been observed at analgesic doses for ultra-rapid metabolisers (code F corresponding to CTCAE grade 5). This results in the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (2 points for code F (CTCAE grade 5)).
Studies confirming an increased risk for severe adverse events (code ≥ D corresponding to CTCAE grade ≥ 3) are lacking. This results in 0 out of the maximum of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (only points for at least one publication with level of evidence score ≥ 3).
The prevalence of CYP2D6 UM in the Netherlands is 1-2%. Thus the number needed to genotype to identify one risk patient is 50 to 100. Because severe adverse events have only been observed in cases, the percentage of ultra-rapid metabolisers developing a severe adverse event is not known, but seems to be low. Thus, the number needed to genotype to prevent a severe adverse event seems considerably larger than 50 to 100. Because the number needed to genotype to prevent 1 adverse event code ≥ D (grade ≥ 3) is likely to be larger than 1000, this results in 0 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG ≤ 1000).
The Dutch drug label indicates that use in patients who are known to be CYP2D6 ultra-rapid metabolisers (UM) is contra-indicated. However, the drug label from the USA states that individuals who are ultra-rapid metabolisers should not use codeine, but does not mention this in the contra-indication section. Neither drug label recommends pre-emptive genotyping. The Dutch drug label results in the maximum number of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the drug label (2 points for at least one genotype/phenotype mentioned as a contra-indication in the corresponding section).
In addition to the clinical implication score indicating pre-emptive genotyping to be beneficial, one cost analysis suggests that maternal CYP2D6 genetic testing to guide treatment for postpartum pain and avert infant adverse events can be cost-effective for specific patient groups (additional costs of $ 10,433 (Canadian dollars) per neonatal central nervous system adverse event averted during maternal treatment for postnatal pain; costs of $ 6627 per averted adverse event when evaluating only subjects having caesarean deliveries). The presumed frequency of UM in this analysis was 8%, which is 4-8 times as high as in the Netherlands, but the probability of codeine given to a subject testing negative for UM or not tested was assumed to be only 0.6584. Thus, pre-emptive genotyping might not only be beneficial, but might also be cost-effective for specific patient groups and this might also be true in the Dutch population.

The table below follows the KNMP definitions for EM, PM, IM and UM. The definitions of EM, PM, IM and UM used in the table below may therefore differ from the definitions used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Baber M et al.	3	Data for the first two days following a Caesarean section were analysed for 96 women from the study of Kelly 2013.	Authors' conclusion: 'In our cohort, poor

<table>
<tr>
<td>The pharmacogenetics of codeine pain relief in the postpartum period.
Pharmacogenomics J
2015;15:430-5.
PubMed PMID: 25752520.</td>
<td>IM: AA
PM: AA
UM: AA</td>
<td>All women received paracetamol/codeine 300/30 mg for use of 1-2 tablets every 4-6 hours, if necessary, during these 2 days. 48% of the women also received naproxen 500 mg twice daily. There was no significant difference in the control of pain and consumption of paracetamol/codeine between women who took and did not take naproxen. Patients recorded pain scores on a visual analogue scale (in mm) 1 hour after each dose of codeine.

Genotyping:
- 60x EM
- 26x IM
- 7x PM
- 3x (UM + gene dose 2.5)

Results:
<table>
<tr><td colspan="3">PM versus IM versus EM versus (UM + gene dose 2.5):</td></tr>
<tr><td></td><td></td><td>value for EM</td></tr>
<tr><td>pain score</td><td>NS</td><td>23.54 mm</td></tr>
<tr><td>mean codeine dose</td><td>NS</td><td>0.82 mg/kg</td></tr>
<tr><td>cumulative codeine dose</td><td>NS</td><td>2.27 mg/kg</td></tr>
</table>
NOTE: it was not specified which gene variants were determined and how the phenotype groups were defined.</td>
<td>metabolizers consumed more codeine cumulatively than intermediate, extensive and ultra-rapid metabolizers, although this was not quite statistically significant.’</td>
</tr>
<tr>
<td>ref. 2
Ray JG et al.
Risk of overdose and death following codeine prescription among immigrants.
J Epidemiol Community Health
2014;68:1057-63.
PubMed PMID: 25104495.</td>
<td>3

UM: AA</td>
<td>30-day rates of overdose or death following medication start in 553,504 new users of codeine or paracetamol/codeine of 6 months or older were calculated with data from databases. Data from Canadian born persons were compared with data from immigrants. The employed medication database contains medication for people aged 65 years and older and younger people with a low income, disability and/or long-term care.
Prevalence of CYP2D6 UM is high (16-28%) in persons of North African, Arab or Eastern African descent. The number of North African or Middle Eastern immigrants in the study was 6011, the number of Eastern African immigrants 2962. Hazard ratios were corrected for age at cohort entry, sex, income quintile, rural versus urban location of residence, number of distinct medications prescribed and physician visits within 12 months preceding cohort entry, being a child of an immigrant mother, and prescription of a CYP2D6 inhibitor (fluoxetine, paroxetine, bupropion, quinidine, cinacalcet, ritonavir or amiodarone) within 120 days before and up to 30 days after the index prescription of codeine.

Results:
<table>
<tr><td colspan="3">30-day rate of overdose or death following start of codeine in comparison with Canadian born persons (↓ means lower risk):</td></tr>
<tr><td>immigrant origin</td><td></td><td>value for Canadian born persons</td></tr>
<tr><td>Eastern Africa</td><td>NS</td><td rowspan="7">57.1/100,000 person-days</td></tr>
<tr><td>North Africa or Middle East</td><td>↓ (S)</td></tr>
<tr><td>other Western nations</td><td>NS</td></tr>
<tr><td>Southeast Asia</td><td>↓ (S)</td></tr>
<tr><td>South Asia</td><td>↓ (S)</td></tr>
<tr><td>Latin America</td><td>↓ (S)</td></tr>
<tr><td colspan="3">Similar effects were seen for 30-day overdose and for 30-day all-cause mortality.
In addition, similar results for Eastern Africa and North Africa or Middle East were seen for age < 50 years.</td></tr>
</table></td>
<td>Authors’ conclusion: ‘Overdose and death following the institution of codeine therapy are not more commonly observed among immigrants from world regions with a high prevalence of ultrarapid CYP2D6 status relative to those born in Canada.’</td>
</tr>
</table>

ref. 2, continuation		When new use of NSAIDs was analysed, decreased risk was found for the two Asian immigrant groups in comparison with Canadian born persons (S). The authors indicate that the lower risk in immigrants might be due to the healthy immigrant effect, in which immigrants are more highly educated than the general population, and/or maintain healthier practices that places them at a lower risk of disease (e.g. less illicit drug use and hazardous drinking).	
ref. 3 Prows CA et al. Codeine-related adverse drug reactions in children following tonsillectomy: a prospective study. Laryngoscope 2014;124:1242-50. PubMed PMID: 24122716.	3	116 Caucasian children of 6-15 years of age received paracetamol/codeine 24/2.4 mg/ml for use every 4 hours with a maximum of 5 doses per 24 hours, as needed, on postoperative day 0 to 3 after outpatient tonsillectomy with or without adenoidectomy. The administered dose was 8/0.8 to 10/1.0 mg/kg with a maximum of 360/36 mg. All 87 children < 45 kg received doses of 8/0.8 to 10/1.0 mg/kg. Parents were advised to use paracetamol/codeine only as a rescue pain medicine and only on an as-needed-basis. 40% of the children had obstructive sleep apnoea. Adverse events were also analysed for 3 UM (one Caucasian > 45 kg and two African American). Perioperative care was standardized (during surgery, doses of intravenous morphine of 0.2 mg/kg and 0.1 mg/kg for patients without and with obstructive sleep apnoea respectively, dexamethasone, and ondansetron; rescue doses of intravenous morphine 0.05 mg/kg or the equivalent of fentanyl in the post anaesthesia care unit). The daily number of adverse events and of paracetamol/codeine doses was measured with an investigator-developed paper dairy. Sedation was measured 45 to 60 minutes after codeine administration with the 0 to 4 University of Michigan sedation scale. For analysis of the effect of genotype on sedation, scores 0-1 (awake) and 2-4 (asleep) were grouped. The genotype effects were measured with linear mixed models. The frequency of adverse events after adjusting for daily number of codeine doses was significantly higher on postoperative day 0 than on the others days. This is likely due to synergistic effects of the first dose of codeine with residual anaesthesia and intravenous opioids. Sedation risk was highest on postoperative day 0 and 1. The most common adverse events were nausea and light-headedness/dizziness in Caucasian children and nausea and vomiting in African American children. Co-medication with CYP2D6-inhibitors was excluded, but CYP2D6/CYP3A4-inductors and CYP3A4-inhibitors were not excluded. Genotyping: Caucasian: - 40x gene dose 2 - 17x gene dose 1.5 - 31x gene dose 1 (1/0) - 5x gene dose 1 (0.5/0.5) - 8x gene dose 0.5 - 14x PM - 1x UM The UM was > 45 kg. African American: - 2x UM Results: PM versus (gene dose 0.5) versus (gene dose 0.5/0.5) versus (gene dose 1/0) versus (gene dose 1.5) versus (gene dose 2) for Caucasian children< 45 kg (n = 87):	Authors' conclusion: 'In a subcohort of white children ≤ 45 kg, increased adverse drug reaction risk was associated with the presence of one or more full function CYP2D6 alleles, postoperative day, and sex. Neither obstructive apnoea nor predicted CYP-2D6 phenotype were associated with sedation risk.'

ref. 3, continuation	PM: AA# IM: AA# 1 UM: B	adverse events: decrease (S) There was also a decrease of adverse events with decreasing gene dose for all Caucasian patients (n = 116, including 1 UM) (S) and for both groups when (gene dose 0-0.5 + gene dose 0.5/0.5) was compared with (gene dose 1.5-2 + gene dose 1/0) (S). The number of adverse events for gene dose 1/0 was comparable to the number for EM, while the number was lower for gene dose 0.5/0.5 (significance not determined). sedation: NS There was also no effect of gene dose for all Caucasian patients (n = 116, including 1 UM) (NS) and for both groups when (gene dose 0-0.5 + gene dose 0.5/0.5) was compared with (gene dose 1.5-2 + gene dose 1/0) (NS). 3 UM: - all reported sedation following a dose of codeine on postoperative day 1 - all reported one or more adverse events on postoperative day 0 to 2 NOTE: genotyping was performed for *2 to *11, *14, *15, *17 to *20, *35, *40 to *42, *44 and gene duplication.	
ref. 4 Kelly LE et al. A clinical tool for reducing central nervous system depression among neonates exposed to codeine through breast milk. PLoS One 2013;8:e70073. PubMed PMID: 23922910.	3 IM: AA PM: AA UM: AA	192 women received paracetamol/codeine 300/30 mg for use every 4-6 hours, if necessary, following a Caesarean section. They were instructed to use the paracetamol/codeine at the lowest possible dose and for no more than 4 days. They were also informed about possible side effects in mother and child and were advised to go to the Accident & Emergency department if the child developed side effects. Genotyping: - 105x EM - 70x IM - 11x PM - 6x UM + gene dose 2.5 Results: - there was no effect of the genotype on the total codeine dose used (NS) - there was no effect of the genotype on the percentage of children with sedation (NS) Neonatal sedation did not occur in any of the UM. However, neonatal sedation was associated with use longer than 4 days and none of the UM used the medication for more than 3 days. - there was no effect of the genotype on the percentage of mothers with side effects (NS) Side effects did not occur in any of the UM. - there was no effect of the genotype on the percentage of patients that stopped taking the paracetamol/codeine due to inadequate effectiveness (NS) NOTE: genotyping was performed for *3 to *10, *12, *14,	Authors' conclusion: 'The only cases of CNS depression occurred when the length of codeine use exceeded the guideline recommendations. Neonatal safety of codeine can be improved using evidence-based guidelines, even in those deemed by genetics to be at high risk for toxicity.'

ref. 4, continuation		*17, *29, *41 and gene duplication (for which the number of copies was determined).	
ref. 5 Kelly LE et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012;129:e1343-7. PubMed PMID: 22492761.	2 UM: F EM: E	3 children received analgesia with codeine following tonsillectomy due to obstructive sleep apnoea. - a 4-year-old boy (27.6 kg) died of respiratory arrest following a total of four doses of 8 mg codeine. The post-mortem codeine concentration was equivalent to that of therapeutic use. However, the morphine concentration was 17.6 ng/mL (therapeutic range is 4.5 ± 2.1 ng/mL). The patient was UM (*1/*2AxN). - a 3-year-old girl (14.4 kg) had to be resuscitated due to respiratory depression following a total of four doses of 15 mg codeine. She made a complete recovery. Her morphine plasma concentration was 17 ng/mL. She was EM (*1/*1). - a 5-year-old boy (29 kg) was discovered lifeless following use of paracetamol with codeine 12 mg every 4 hours (2.5 mg/kg per day). The post-mortem morphine plasma concentration was 30 ng/mL and the codeine plasma concentration was 79 ng/mL. The genotype was not determined, but the high morphine/codeine ratio suggests a UM genotype.	Authors' conclusion: 'In 2009 we reported the fatal case of a toddler who had received codeine after adenotonsillectomy for obstructive sleep apnea syndrome. The child was an ultra-rapid metabolizer of CYP2D6. We now report 3 additional fatal or life-threatening cases from North America.'
ref. 6 Sistonen J et al. Prediction of codeine toxicity in infants and their mothers using a novel combination of maternal genetic markers. Clin Pharmacol Ther 2012;91:692-9. PubMed PMID: 22398969.	3 PM: AA# UM: C	111 mothers used codeine after giving birth and were breastfeeding. Relevant co-medication was not excluded. Similar results were obtained following correction for codeine dose and age of the mother. Genotyping: - 94x EM + gene dose 1 - 12x PM + gene dose 0.5 - 5x UM + gene dose 2.5 (5x one extra copy) (PM + gene dose 0.5) versus (EM + gene dose 1) versus (UM + gene dose 2.5): - decrease in the risk of central nervous system depression in the child (OR = 4.19; 95% CI: 1.04 - 16.80) (S) The difference between (UM + gene dose 2.5) and (EM + gene dose 1) is significant (OR = 4.9; 95% CI: 2.7 - 9.1) (S). - decrease in the risk of central nervous system depression in the mother (OR = 8.62; 95% CI: 1.62 - 45.80) (S) NOTE: genotyping was performed for *2 to *10, *12, *14, *17, *29, *41 and gene duplication (for which the number of copies was determined).	Authors' conclusion: 'A genetic model combining the maternal risk genotypes in CYP2D6 and ABCB1 was significantly associated with the adverse outcomes in infants (OR 2.68) and their mothers (OR 2.74). A novel combination of the genetic and clinical factors predicted 87% of the infant and maternal CNS depression cases with a sensitivity of 80% and a specificity of 87%.'
ref. 7 VanderVaart S et al. CYP2D6 polymorphisms and codeine analgesia in postpartum pain management: a pilot study. Ther Drug Monit 2011;33:425-32. PubMed PMID: 21743374.	3	45 mothers used paracetamol/codeine/caffeine 300:30:15 mg at a dose of 1-2 tablets every 4 hours, if necessary, for breakthrough pain in the 3 days following a Caesarean section. The women used naproxen 500 mg every 12 hours for the first 2 days. They used paracetamol 500 mg at a dose of 1-2 tablets every 4 hours, if necessary, for mild to moderate pain. CYP2D6 and CYP3A4 inhibitors were excluded. Similar results were obtained after correction for body weight-corrected codeine and naproxen doses, age of the mother and birth weight of the child. Genotyping: - 14x EM - 26x IM + gene dose 1.5 (5x gene dose 0.5; 11x gene dose 1; 10x gene dose 1.5) - 2x PM - 3x UM + gene dose ≥ 2 (2x gene dose ≥ 3, 1x gene dose ≥ 2)	Authors' conclusion: 'In this pilot study, the extreme CYP-2D6 genotypes (PMs and UMs) seemed to predict pain response and adverse events.'

ref. 7, continuation	IM: AA 2 UM: C 2 PM: B	(UM + gene dose ≥ 2) versus EM versus (IM + gene dose 1.5) versus PM: - no significant difference in pain scores (NS) The pain scores were higher for UM (NS). - no significant difference in total codeine dose (NS) The dose was higher for PM (NS). UM: - each of the 3 UM had a factor associated with increased pain after Caesarean section (young age or a baby heavier than 4 kg) - 2 UM used very little codeine (1x and 3x 60 mg). They preferred naproxen and/or paracetamol for analgesia, due to dizziness and constipation caused by codeine. - the third UM was not prescribed naproxen. She used 9x 60 mg codeine in three days. She reported no side effects, but had not had a bowel movement 3 days post surgery. PM: - both PMs did not have any factors associated with recurrence of pain after Caesarean section - both indicated no reduction in pain after use of codeine. One PM switched to paracetamol after 2 doses of 60 mg. The other used 13x 60 mg over 3 days. She reported no side effects, but had not had a bowel movement 3 days post surgery. The authors stated that the study was too small to determine the relationship between genotype and pain score. NOTE: genotyping was performed for *2 to *10, *12, *14, *17, *29, *41 and gene duplication.	
ref. 8 Ciszkowski C et al. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med 2009;361:827-8. PubMed PMID: 19692698.	2 UM: F	A 2-year-old boy (13 kg) received analgesia with codeine following tonsillectomy due to obstructive sleep apnoea. The boy died after 2.5 days due to bronchopneumonia. The prescribed analgesic was codeine 10-12.5 mg and paracetamol 120 mg every 4-6 hours, if necessary. The authors indicated that this was within the recommended dose of 1-3 mg/kg per day. The post-mortem codeine plasma concentration was 0.7 ng/mL and the morphine plasma concentration was 32 ng/mL. Respiratory depression can occur in young children at morphine concentrations from 20 ng/mL. The boy was a UM.	Authors' conclusion: 'Because of the polymorphic nature of codeine metabolism and the fact that adenotonsillectomy does not reverse all cases of obstructive sleep apnea, codeine cannot be considered a safe outpatient analgesic for young children after adenotonsillectomy.'
ref. 9 Madadi P et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. Clin Pharmacol Ther 2009;85:31-5.	3 UM: C (2)	72 mothers who used codeine and were breastfeeding, with 17 cases in which the child exhibited signs of central nervous system depression. - The prevalence of UM was 6x higher in the cases than in the controls (11.8% versus 1.8%) (NS). In addition, the child of the only UM in the control group was 6 months old and was receiving formula milk and solids in addition to breast milk during the mother's codeine use. - One of the UM cases was described in Koren, 2006. The other case was a woman who used codeine 120 mg/day after giving birth. She was experiencing side effects and on day 7 the child became extremely drowsy and was feeding poorly. She was already supplementing with formula milk from day 1 and stopped breastfeeding all	Authors' conclusion: 'Breastfed infants of mothers who are CYP2D6 UMs combined with the UGT2B7*2/*2 are at increased risk of potentially life-threatening CNS depression.'

ref. 9, continuation		together on day 7, after which the baby recovered. Both cases were CYP2D6 UM and UGT2B7*2/*2.	
ref. 10 Kirchheiner J et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J 2007;7:257-65.	3 PM: A (UM + EM): A	26 healthy volunteers, 3x PM (1x *3/*3, 2x *4/*4), 11x EM (4x *1/*1, 3x *1/*2, 1x *1/*9, 1x *1/*10, 1x *2/*41, 1x *35/*41), 12x UM + EM (1x *1/*35, 1x *1x2/*9, 1x *1x2/*10, 1x *1x2/*41, 1x *2x2/*41, 1x *35x2/*1, 2x *2x2/*35, *1x 1x2/*35, 2x *2x2/*1, 1x *1x2/*1), single dose of 30 mg codeine, no co-medication; *kinetic endpoints* - PM: decrease in AUC codeine versus EM from 191 to 180 µg·h/L (NS by 6%), decrease in AUC morphine from 11 to 0.5 µg·h/L (S by 2100%). T½ codeine is 4.8 hours, T½ morphine is 17 hours. - UM + EM: no change in AUC codeine versus EM, increase in AUC morphine from 11 to 16 µg·h/L (S by 45%). T½ codeine is 3.7 hours, T½ morphine is 14 hours. CYP2D6 genotype explains 60%-63% of the variability in AUC morphine. *clinical endpoints* - PM: greater decrease in pupil diameter (measure of effect on µ-opioid receptors) than for EM, difference was non-significant. A total of 66% experienced side effects, increase by 57% versus EM, S. - UM + EM: non-significant change in pupil diameter versus EM. Increase in all side effects versus EM from 42% to 100%, 91% of the UMs experienced sedation versus 50% of the EMs (NS by 82%). NOTE: One EM was heterozygous for the µ-opioid receptor gene.	Authors' conclusion: 'No severe adverse effects were seen in the UMs in our study most likely because we used for safety reasons a low dose of only 30 mg.' AUC morphine versus EM: PM: 5% UM + EM: 145% AUC codeine versus EM: PM: 94% UM + EM: 100%
ref. 11 Koren G et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006;368:704.	2 UM: F§	Neonate was breastfeeding from mother who used codeine, 60 mg/day, 1st two days 120 mg/day. On day 7, the neonate became lethargic and was struggling to feed. Recovery on day 11, followed by recurrence of problems with breastfeeding on day 12 and grey discolouration of the skin. Neonate died on day 13. The neonate's post-mortem morphine plasma concentration was 70 ng/mL (normal 0-2.2 ng/mL). The morphine concentration in the breast milk on day 10 was 87 ng/mL (normally 1.9-20.5 ng/mL with use of 60 mg/6 hours). Mother is UM (duplication *2: 2x *2).	Authors' conclusion: 'This case shows that polymorphism of CYP2D6 can be life threatening for some breastfed babies.'
ref. 12 Gasche Y et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004 30;351:2827-31.	2 UM: D	Patient with reduced renal function and pneumonia received antibiotics and codeine 25 mg 3x/day to combat cough, co-medication: CYP3A4 inhibitors: symptoms of opiate intoxication, became comatose after 4 days. Naloxone resulted in dramatic improvement. Patient was found to be UM (3 or more duplications, MR-dextromethorphan << 0.0005). Morphine plasma concentration was 80 µg/mL (normal is 1-4 µg/mL), M3G and M6G were also elevated. Intoxication is probably the result of the CYP2D6 UM phenotype in combination with two CYP3A4 inhibitors and reduced renal function. It is worth noting that the codeine concentration was also elevated.	
ref. 13 Williams DG et al. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for	3	96 children with adenotonsillectomy, 48x codeine, 2x PM (2 dysfunctional alleles), 9x IM/PM (1 dysfunctional allele and 1 reduced functional allele), 17x IM (2x reduced functional allele), 19x EM (2 functional alleles or 1 functional allele and 1 reduced functional allele), screened for *1 to *5, *9, *10 and *17 alleles, single dose of codeine 1.5 mg/kg, co-medication diclofenac, measurement 1 hour after administration;	Authors' conclusion: 'Codeine analgesia is less reliable than morphine, but was not well correlated with either phenotype or plasma mor-

analgesic reliability. Br J Anaesth 2002;89:839-45. **ref. 13, continuation**	IM: A PM: AA	- IM and IM/PM: morphine concentration was reduced by approx. 15% versus EM (S). - PM: no detectable morphine. No relationship either between phenotype and need for extra pain medication, or between concentration of morphine/metabolites and need for extra pain medication.	phine in this study.'
ref. 14 Poulsen L et al. Codeine in post-operative pain. Study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide. Eur J Clin Pharmacol 1998;54:451-4.	3 PM A	81 patients with post-operative pain, 74 phenotyped (sparteine), 8x PM and 66x EM, single dose of 100 mg codeine, no CYP2D6 inhibitors as co-medication, measurement 1 hour after administration; - PM: morphine and M6G below detection limit. Reduction in pain differed non-significantly from EM. Trend towards reduction in pain with concentration of morphine + M6G < 10 nM being smaller than with concentration > 10 nM (NS). No correlation between pain reduction and concentration of morphine + M6G. NOTE: use of rescue medication was permitted NOTE: genotype unknown	Authors' conclusion: 'With the overall low efficacy of codeine …it is very difficult to detect subgroup differences in effect. …Together with the fact that the number of PM was small, it is not surprising that there was no statistically significant difference in analgesic effect between PM and EM.'
ref. 15 Eckhardt K et al. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. Pain 1998;76:27-33.	3 PM: B	18 volunteers, 9x PM (6x *4/*4, 1x *3/*5, 1x *4/*5) and 9x EM (2x *1/*1, 4x *1/*2, 1x *1/*10, 1x *1/*5, 1x *2/*3), single dose of 170 mg codeine, no co-medication, measurement after 25 hours; *kinetic endpoints* - PM: decrease in AUC of morphine from 173 to 10 nM·hr versus EM (S by 94%), T½ is 5.0 hours. Increase in AUC for codeine from 4014 to 5140 nM·hr (NS by 28%), T½ is 3.8 hours. *clinical endpoints* - PM: number of side effects differed non-significantly from EM, pain tolerance differed non-significantly from placebo. - EM: pain tolerance is elevated by 1293% versus placebo (S).	Authors' conclusion: 'Suggesting that PMs showing no analgesic effects from codeine doses up to 170 mg implicates that 7-10% of the Caucasian population will have no analgesic benefit after codeine administration but may suffer side effects caused by codeine itself.' AUC morphine versus EM: PM: 6% AUC codeine versus EM: PM: 128%
ref. 16 Dalen P et al. Quick onset of severe abdominal pain after codeine in an ultrarapid metabolizer of debrisoquine. Ther Drug Monit 1997;19:543-4.	2 UM: B	Patient received 1 g paracetamol + 60 mg codeine, developed severe pain in upper abdomen, euphoria and dizziness after 30 min., symptoms persisted for 3-4 hours. When "re-challenged" with 30 mg codeine, the same symptoms occurred to a lesser extent. Phenotyping and genotyping revealed that the patient was UM (MR-debrisoquine is 0.1, duplication *2).	
ref. 17 Mikus G et al. Effect of codeine on gastrointestinal motility in relation to CYP2D6 phenotype. Clin Pharmacol Ther 1997;61:459-66.	3 PM: A	10 volunteers, 5x PM (3x *4/*4, 1x *3/*34, 1x *5/*5) and 5x EM (2x *1/*1, 3x *1/*4), single dose of 60 mg codeine, no co-medication; *kinetic endpoints* - PM: decrease in AUC for codeine from 1440 to 1338 pmol/mL·hr versus EM (NS by 7%), T½ is 2.3 hours. For morphine, the AUC ratio decreased from 27.8 to 1.9 pmol/mL·hr (S by 93%), T½ is 4.8 hours. *clinical endpoints* - PM: transition time from mouth to appendix differs non-	AUC morphine versus EM: PM: 7% AUC codeine versus EM: PM: 93%

ref. 17, continuation		significantly for codeine versus placebo. - EM: transition time from mouth to appendix differs significantly for codeine versus placebo.	
ref. 18 Hasselstrom J et al. The effect of codeine on gastrointestinal transit in extensive and poor metabolisers of debrisoquine. Eur J Clin Pharmacol 1997;53:145-8.	3 PM: AA	24 volunteers, 12x PM and 12x EM (MR-debrisoquine < 1), single dose of 50 mg codeine, no co-medication; Transition time from mouth to appendix differs non-significantly between PM and EM.	
ref. 19 Tseng CY et al. Formation of morphine from codeine in Chinese subjects of different CYP2D6 genotypes. Clin Pharmacol Ther 1996;60:177-82.	3 IM: AA	32 volunteers, (12x *10/*10, 12x *1/*10, 8x *1/*1), single dose of 30 mg codeine, no co-medication: - *10/*10: increase in AUC for codeine from 938 to 998 nM·hr versus *1/*1 (NS by 6%), T½ is 2.3 hours. - *1/*10: increase in AUC for codeine from 938 to 966 nM·hr versus *1/*1 (NS by 3%), T½ is 2.5 hours.	
ref. 20 Poulsen L et al. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. Eur J Clin Pharmacol 1996;51:289-95.	3 PM: B	28 volunteers, 14x PM and 14x EM (phenotyped with sparteine), single dose of 75-100 mg codeine, no co-medication, pain measurement using “cold pressor test” and heat & pressure stimulation 1-4 hours after administration: *kinetic endpoints* - PM: increase in $AUC_{0\text{-}4.5hr}$ of codeine from 1427 to 1569 nM·hr versus EM (NS by 10%); morphine and M6G are below the detection limit in 13 of the 14 PMs. *clinical endpoints* - PM: no difference versus placebo in the occurrence of side effects or in the three pain tests - EM: more side effects (S) versus placebo and difference in the cold pressor test.	
ref. 21 Persson K et al. Patient-controlled analgesia (PCA) with codeine for post-operative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. Br J Clin Pharmacol 1995;39:182-6.	3 PM: AA	11 post-operative patients admitted for hysterectomy, 1x PM, 10x EM (phenotyped with dextromethorphan), 10 mg codeine i.v. each time via PCA, co-medication during surgery; Inadequate analgesia for 2 patients, 1x PM, 1x EM with severe hip fracture.	
ref. 22 Yue QY et al. Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. Br J Clin Pharmacol 1991;31:635-42.	4 PM: A	20 volunteers, 9x PM and 11x EM (phenotyped with debrisoquine), single dose of 50 mg codeine for 6x PM and 8x EM, 50 mg codeine every 6 hours for 54 hours in 3x PM and 3x EM, no co-medication; single dose: - PM: AUC of codeine unchanged, T½ is 2.9 hours. Morphine was above the detection limit in only 1 PM. Decrease in AUC of M6G from 117 to 5.2 nM·hr versus EM (S by 96%). The AUC of M3G and normorphine were also reduced (S). - EM: AUC codeine is 1010 nM·hour, T½ is 2.43 hours, AUC M6G is 117 nM·hour. comparable results were obtained for multiple dosing. NOTE: genotype unknown.	
ref. 23 Desmeules J et al. Impact of	3	8 volunteers, 1x PM and 7x EM (phenotyped with dextromethorphan), single dose of 100 mg codeine, co-medication unknown;	Authors’ conclusion: ‘In PM of genetic origin, or due to en-

environmental and genetic factors on codeine analgesia. Eur J Clin Pharmacol 1991;41:23-6. **ref. 23, continuation**	PM: B	*kinetic endpoint* - PM: AUC of morphine is below the detection limit. *clinical endpoint* (pain threshold with calf nerve stimulation) - PM: for the subjective and objective pain threshold, no effect was found with codeine. - EM: the subjective and objective pain threshold were elevated versus placebo for 2 hours after administration (S). NOTE: genotype unknown	vironmental alteration of the phenotypic expression (i.e. drug interaction), codeine is not activated into morphine and is an inefficient analgesic.'
ref. 24 Sindrup SH et al. Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. Clin Pharmacol Ther 1990;48:686-93.	3 PM: B	24 volunteers, 12x PM and 12x EM (phenotyped with sparteine), single dose of 75 mg codeine, measurement after 1 week wash-out, no co-medication; *kinetic endpoint* - PM: concentration of codeine is reduced versus EM (NS). Concentration of morphine is below the detection limit. *clinical endpoint* (pain threshold with laser stimulation 90, 150 and 210 min. after administration) - PM: pain threshold changes non-significantly after 90, 150 and 210 min. versus before administration. - EM: pain threshold is significantly increased 90 and 150 minutes after administration of codeine. There is a correlation between the C_{ss} of morphine and the effect on the pain threshold (S). NOTE: genotype unknown	Authors' conclusion: 'This study showed that codeine increased pain thresholds to laser stimuli in extensive metabolizers but not in poor metabolizers. Thus in poor metabolizers the analgesic activity to codeine is either absent or at least much weaker than in extensive metabolizers.'
ref. 25 European Medicines Agency. Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation. 28-06-13.	0 UM: F	The EMA has decided to expand the contra-indications for codeine. The change will be implemented by all member states according to an agreed timetable. Codeine is currently contra-indicated: - for all patients who are CYP2D6 ultra-rapid metabolisers (approximately 10% of Caucasians), because the risk of developing severe and life-threatening side effects is elevated - for all paediatric patients undergoing tonsillectomy and/or adenoidectomy due to obstructive sleep apnoea - for women who are breastfeeding This decision follows an assessment of the available safety and effectiveness data for use of codeine in children. This assessment revealed the following data relating to CYP2D6 polymorphisms: In 6 cases of respiratory depression (including 3 fatal cases) in children treated with codeine at recommended doses following tonsillectomy for obstructive sleep apnoea, some of these children were found to be CYP2D6 ultra-rapid metabolisers. Furthermore, a published case of fatal respiratory depression describes an infant whose codeine-using mother was a CYP2D6 ultra-rapid metaboliser.	
ref. 26 SmPC Codeine phosphate Ratiopharm 02-03-16.	0 IM: B PM: B	<u>CI</u>: use in patients who are known to be CYP2D6 ultra-rapid metabolisers. <u>Warning</u>: The liver enzyme CYP2D6 converts codeine into its active metabolite morphine. If a patient is deficient for or lacks this enzyme, a sufficient therapeutic effect will not be reached. It is estimated that 7% of the Caucasian population has this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser, the risk for development of adverse events of opioid toxicity is increased, even at usually prescribed doses. These patients convert codeine more rapidly into morphine, resulting in higher than expected morphine serum concentrations. General symptoms of opioid toxicity are confusion, sleepiness, shallow breathing, narrowed pupils, nausea, vomiting, constipation and lack of appetite. In serious cases, symptoms of circulatory and respiratory	

ref. 26, continuation	UM: F	depression can occur, which can be life threatening and fatal in rare cases. Breastfeeding: Codeine is contraindicated in breastfeeding mothers. If a patient is a CYP2D6 ultra-rapid metaboliser, higher concentrations of the active metabolite morphine can be present in the breast milk and in very rare cases lead to symptoms of opioid toxicity in the infant, which can be fatal. Pharmacokinetics: *Special patient groups: CYP2D6 polymorphism* As a result of genetic variation, approximately 7% of the Caucasian population has a non-functioning CYP2D6 enzyme. This can result in reduced analgesic effect of codeine in these patients, because no morphine is formed. In addition, 1-5% of the Caucasian population has increased activity of the CYP2D6 enzyme. These patients can have elevated plasma concentrations of morphine and side effects of morphine can occur, particularly in patients with reduced renal function, because the active metabolite morphine-6-glucuronide is excreted to a lesser extent. Increased CYP2D6 enzyme activity is more common in African and Mediterranean population groups.	
ref. 27 SmPC Codeine Sulfate Tablets 29-08-17, USA.	0 UM: F	Boxed warning: *Ultra-rapid metabolism of codeine and other risk factors for life-threatening respiratory depression in children* Life-threatening respiratory depression and death have occurred in children who received codeine; most cases followed tonsillectomy and/or adenoidectomy and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism. Codeine Sulfate Tablets are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Avoid the use of Codeine Sulfate Tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. Warning: *Ultra-rapid metabolism of codeine and other risk factors for life-threatening respiratory depression in children* Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death: • Codeine Sulfate Tablets are contraindicated for all children younger than 12 years of age. • Codeine Sulfate Tablets are contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy. • Avoid the use of Codeine Sulfate Tablets in adolescents	

ref. 27, continuation		12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression. • As with adults, when prescribing codeine for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose. *Nursing mothers* At least one death was reported in a nursing infants who was exposed to high levels of morphine in breast milk because the mothers was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with Codeine Sulfate Tablets. *CYP2D6 genetic variability: ultra-rapid metabolizers* Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g. gene duplications denoted as *1/*1xN or *1/*2xN). These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). Therefore, individuals who are ultra-rapid metabolizers should not use Codeine Sulfate Tablets. <u>Use in specific populations</u>: *Lactation* Risk summary Codeine and its active metabolite, morphine, are present in human milk. There are published studies and cases that have reported excessive sedation, respiratory depression, and death in infants exposed to codeine via breast milk. Women 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 in their breastfed infants. Because of the potential for serious adverse reactions, including excess sedation, respiratory depression, and death in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Codeine Sulfate Tablets. Clinical Considerations If infants are exposed to Codeine Sulfate Tablets through breast milk, they should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped. *Paediatric use* The safety and effectiveness of Codeine Sulfate tablets in pediatric patients have not been established. Life-threatening respiratory depression and death have occurred in children who received codeine. In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with sleep apnea	

ref. 27, continuation		may be particularly sensitive to the respiratory depressant effects of codeine. Because of the risk of life-threatening respiratory depression and death: • Codeine Sulfate Tablets are contraindicated for all children younger than 12 years of age. • Codeine Sulfate Tablets are contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy. • Avoid the use of Codeine Sulfate Tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory. <u>Adverse events</u>: The following serious adverse reaction is described, or described in greater detail, in other sections: ultra-rapid metabolism of codeine and other risk factors for life-threatening respiratory depression in children.	

§ effect on neonate, mother is UM and uses codeine.
AA#: There is a significant effect, but this effect is positive rather than negative.

Risk group	IMs with CYP2D6 inhibitor, UMs with CYP3A4 inhibitor

Comments:

- Studies in which only concentrations in urine were measured were not included in this status report. Articles from 2007 onwards that only mentioned ratios and not concentrations or AUCs of the individual substances, or which included insufficient data to distinguish between PM, IM, EM and UM in the study population (for example, investigation of gene dose smaller than or equal to 1.5), were not included in this status report. Articles from 2009 onwards with only kinetic endpoints were not included, because they do not contribute sufficiently to the burden of proof. Recommendations for dose adjustment are not useful for codeine. For IM and PM, the enzyme activity is the limiting factor in the formation of morphine and use by UM for analgesia is now contra-indicated.
- <u>Existing guidelines</u>:
  - Crews KR et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Clin Pharmacol Ther 2012;91:321-6. PubMed PMID: 22205192
    and
    Crews KR et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 2014;95:376-82. PubMed PMID: 24458010.
    CPIC uses the same definition for PM as we do. However, CPIC uses other definitions for EM (gene dose 1-2), IM (gene dose 0.5) and UM (gene dose ≥ 2.5). In the recommendations below, the KNMP definitions for EM, PM, IM and UM are used. CPIC indicates that classifying patients with an activity score of 1.0 as EMs in this guideline is based on data specific for formation of morphine from codeine in these patients (Lötsch J et al. Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? Pain 2009;144:119-24).
    Half of the literature on kinetic effects of CYPD6 gene variants analysed by CPIC is also included in our risk analysis, as is threequarter of the literature on clinical effects.
    CPIC indicates that the association of CYP2D6 metaboliser phenotype with the formation of morphine from codeine is well defined and that there is substantial evidence linking CYP2D6 genotype to variability in codeine efficacy and toxicity. Pharmacokinetic and pharmacodynamic studies show a decrease in morphine levels and a decrease in analgesia in PMs receiving codeine as compared with EMs (Eckhardt 1998, Lötsch J et al. Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? Pain 2009;144:119-24, and other studies). A decreased incidence of gastrointestinal side effects (i.e., constipation) was reported in PMs versus EMs (Mikus 1997), whereas a later study by the same group of investigators found that central side effects (e.g., sedation, nausea, and dry mouth) did not differ between PMs and

EMs (Eckhardt 1998). CPIC indicates that there is insufficient evidence in the literature to recommend a higher dose of codeine in poor metabolizers, especially considering the evidence in this latter paper that select adverse effects do not differ between PMs and EMs.
In addition, CPIC indicates that pharmacokinetic studies show increased conversion of codeine to morphine in CYP2D6 UMs versus PMs (Kirchheiner 2007), which can result in toxic systemic concentrations of morphine (Gasche 2004) even at low codeine doses. However, it should be noted that there is a large amount of variability within the patients genotyped as EMs (Kirchheiner 2007), and it is possible that some of these subjects may develop symptoms similar to those of patients genotyped as UMs (Kelly 2012). The genomic or environmental mechanisms causing considerable variation among individuals with the same diplotype are unknown. Case reports detail the occurrence of severe or life-threatening side effects following standard doses of codeine in UMs (Dalen 1997, Gasche 2004 and Ciszkowski 2009).
Based on the data above, CPIC recommends using alternative analgesics to codeine in patients who are CYP2D6 PMs or UMs. They indicate, that it is important to recognize that in addition to codeine, several other opioids are metabolised, at least in part, by CYP2D6. The opioids tramadol, hydrocodone, and oxycodone are *O*-demethylated by CYP2D6 to *O*-desmethyltramadol, hydromorphone, and oxymorphone, respectively (Stamer UM et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP-2D6 genotypes. Clin Pharmacol Ther 2007;82:41-7 and Lalovic B et al. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. Clin Pharmacol Ther 2006;79:461-79). The CPIC recommendations are summarized in the table below.

Phenotype/ genotype group	**Recommendation**	**Classification of the recommendation**	**Considerations for alternative opioids**
UM + gene dose 2.5	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[a,b]
Gene dose 1-2	Use label-recommended age- or weight-specific dosing.	Strong	
Gene dose 0.5	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics, such as morphine or a non-opioid.	Moderate	Monitor tramadol use for response.
PM	Avoid codeine due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.

[a] There is substantial evidence for decreased efficacy of tramadol in PMs and a single case report of toxicity in an UM with renal impairment following tramadol use post-surgery. Use of other analgesics in CYP2D6 PMs and UMs may therefore be preferable.

[b] Some other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with non-opioid analgesics, may be considered as alternatives for use in CYP2D6 PMs and UMs.

The recommendations above are still the same after the last update on 20-4-2017 on the PharmGKB-site.

- US Food and Drug Administration. FDA Drug Safety Communication 20-2-2013. Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. http://www.fda.gov/drugs/drugsafety/ucm339112.htm

Information for health care professionals:

- Deaths have occurred in children with obstructive sleep apnoea who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolisers of codeine due to a cyto-

chrome P450 2D6 (CYP2D6) polymorphism. These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine.
- Routine CYP2D6 genotype testing is not being recommended for use in this setting because patients with normal metabolism may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolisers.

Data summary:

A search of FDA's Adverse Event Reporting System database between 1969 to May 1, 2012 identified 13 cases of paediatric death (n=10) or overdose (n=3) associated with codeine. Seven of these cases were also described in the medical literature (Voronov P et al. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. Paediatr Anaesth 2007;17:684-7; Hermanns-Clausen M et al. Drug dosing error with drops: severe clinical course of codeine intoxication in twins. Eur J Pediatr 2009;168:819-24; Ciszkowski 2009 and Kelly LE 2012). The patients ranged in age from 21 months to 9 years. Most of the cases (11/13) were reported in the setting of adenotonsillectomy (n=8) or respiratory tract infection (n=3). In most of these cases, the children appeared to receive appropriate doses of codeine. Cytochrome P450 2D6 (CYP2D6) metaboliser status was mentioned for the seven children described in the literature. Three children were characterized as ultra-rapid metabolisers, three as extensive metabolisers, and one as a likely ultra-rapid metaboliser.

FDA also sought to identify additional cases from other data sources. FDA reviewed a physician survey of mortality and major morbidity following tonsillectomy and/or adenoidectomy conducted by the American Academy of Otolaryngology-Head and Neck Surgery. Limited information was available from these cases; however, one 3-year-old patient with obstructive sleep apnoea who died after adenotonsillectomy was confirmed as being an ultra-rapid metabolizer, and one 12-year-old patient with obstructive sleep apnoea who died after adenotonsillectomy was suspected of being an ultra-rapid metabolizer after high blood morphine levels were identified on autopsy (Goldman JL et al. Mortality and major morbidity after tonsillectomy: etiologic factors and strategies for prevention. Laryngoscope 2013. In press).

- Cost-effectiveness:

Moretti ME et al. A cost-effectiveness analysis of maternal CYP2D6 genetic testing to guide treatment for postpartum pain and avert infant adverse events. Pharmacogenomics J 2017 Jul 11 [Epub ahead of print]. PubMed PMID: 28696420.

The study compared the costs of pharmacogenetically guided therapy for postnatal pain with standard care in a hypothetical cohort of pregnant patients who were anticipated to require analgesia after delivery, planned to breast feed and did not take any other medications which may have similar adverse effects on the breastfed infant. The authors calculated the costs to be $ 10,433 (Canadian dollars) for genotyping compared to no genotyping per neonatal central nervous system adverse event averted during maternal treatment for postnatal pain. Results were sensitive to hospital admission costs. The costs were lower when evaluating only subjects having caesarean deliveries ($ 6627 per averted adverse event) or those from ethnic populations known to have a high prevalence of ultra-rapid metabolisers. The authors conclude that, although genotyping to guide pharmacotherapy was not cost saving, the cost to avert an infant adverse event may represent good value for money in specific populations. The presumed frequency of UM was 8%. This is higher than the 1% to 2% found in the Netherlands. When the probability of codeine use was lower than 0.53 the genotyping strategy cost more money without reducing the number of averted adverse events.

Pharmacogenetically guided therapy consisted of screening prior to delivery and using the result to guide analgesia prescriptions after delivery. Women who tested positive for the UM phenotype were given only non-codeine analgesics while breastfeeding. Standard care consisted of no routine genotyping and analgesia administration after delivery as per local practice patterns. Local practice patterns depended on the prescribing habits and discretion of the attending physician, but generally, all patients who required analgesia were prescribed paracetamol and non-steroidal anti-inflammatory drugs followed by paracetamol/opiate combination as needed in a stepwise sequence.

Calculations were from a societal perspective. All direct health care costs and loss of productivity to the mothers and their family or caregivers, resulting from an adverse event, were calculated. Results from a health care system were similar. The time horizon of the analysis was extending from the genotype screening prior to delivery to the resolution of any postpartum adverse events, typically < 1 month after delivery. The model was populated with inputs from published literature. All inputs were vetted by clinical experts in terms of current face validity and plausibility. The additional costs of genotyping were $ 353 per patient and genotyping reduced the number of adverse events with 0.0339 per patient. The calculation was based on genotyping costs (including shipping and post-test consultation) of $ 381.89 per patient, costs of two tablets of codeine/paracetamol 30/325 mg prescribed every 4 h as needed of $ 0.3980 per patient per day, costs of additional analgesics used as polytherapy with opioids of $ 1.1500 per patient per day, costs of other analgesics used by non-opioid users of $ 0.9615 per patient per day, costs of a call by parent for help or consultation to the Teratology Information Service of $ 42.00 per adverse event, costs of emergency room admission (ambulance, emergency room visit, emergency physician) of $ 615.98, costs of hospital admission of $ 6865 per patient, costs of in-patient physician visit for day one of $ 196.28 per patient and for subsequent days of $ 58.80 per patient per day, parent lost productivity costs for time missed from work/usual activities to be in emergency room or hospital with child of $ 250.23 per day, a probability of being UM of 0.08, a probability of receiving codeine given subject tested

positive for UM of 0, a probability of codeine given subject tested negative for UM or was not tested of 0.6584, a probability of an adverse event given non-codeine (metaboliser status unknown) of 0, a probability of an adverse event given codeine use and UM of 0.6667, a probability of an adverse event given codeine use and non-UM of 0.2174, a probability of emergency room visit with an adverse event of 0.1143, a probability of hospital admission with emergency room visit given an adverse event of 0.9, a probability of UM for testing positive for UM (true positive) of 0.99 and a probability for non-UM for testing non-UM (true negative) of 0.999. It was assumed that women exclusively breastfed their infants during the interval of drug use. Only the first postnatal adverse event in the infant was included and was limited to central nervous system depressive events such as sedation, lethargy, irregular breathing, decreased alertness and poor feeding. Part of the data were derived from Kelly 2013.
Variation of the input parameters within pre-specified borders showed that in 97% of simulations genotyping costs more than standard care. In 72.8% of simulations, genotyping resulted in less adverse events. The model was sensitive only to a single variable: the costs of hospital admission. When hospital admission costs associated with a severe adverse event were greater than $104,000 per stay, the genotyping strategy became cost saving. When costs of hospital admission were less than $ 80,000 the no genotyping strategy was preferred, even when the probability of an adverse event was extremely high. When the probability of codeine use was lower than 0.53 the genotyping strategy cost more money without reducing the number of averted adverse events.
When the model was run for a group of patients with an UM prevalence of 40%, the genotyping strategy cost $192 per patient more and averted 0.1743 adverse events per patient, resulting in costs of $ 1104 per averted adverse event. In a second scenario, that of a group of patients delivering by caesarean section only, the genotyping strategy cost $ 346 per patient more and averted 0.0522 adverse events per patient, resulting in additional costs of $ 6627 per averted adverse event. As patients with surgical deliveries are more likely to experience pain and therefore more likely to use opioids, the rate of opioid use was increased to 93% for this scenario. Moreover, because infants born by caesarean section may be more prone to adverse events in the days after birth, the probability of an adverse event was increased to 0.2174.

Date of literature search: 18 October 2017.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
Dutch Pharmaco-genetics Working Group Decision	PM	4 B	yes	yes	20 November 2017
	IM	3 A	yes	yes	
	UM	3 F	yes	yes	

Mechanism:
Codeine is primarily metabolised by glucuronidation, CYP3A4 and CYP2D6. Conversion by CYP2D6 results in formation of the active metabolite morphine, which has a 200x higher affinity for the μ-opioid receptor than codeine itself. Morphine is further converted to morphine-3-glucuronide and the active morphine-6-glucuronide. Conversion by CYP3A4 results in formation of the metabolite norcodeine, which does not have a therapeutic activity at the μ-opioid receptor.
A CYP2D6 genetic polymorphism may cause a change in the plasma concentration of codeine, morphine and morphine-6-glucuronide.