CYP2D6: tramadol 1589/1590/1591

AUC = area under the concentration-time curve, CI = confidence interval, C_{max} = maximum plasma concentration, 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), MR = metabolic ratio, *N*-DT = *N*-desmethyltramadol, NS = non-significant, *O*-DT = *O*-desmethyltramadol, OR_{corr} = odds ratio, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, UM = ultra-rapid metaboliser (gene dose ≥ 3) (enhanced CYP-2D6 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:

Tramadol is metabolised by CYP2D6, CYP3A4 and by glucuronidation. Conversion by CYP2D6 results in formation of the active metabolite *O*-desmethyltramadol, which has a 300x higher affinity for the μ-opioid receptor than the mother substance. Tramadol itself has an analgesic effect through inhibition of the re-uptake of norepinephrine and serotonin. When the ratio of tramadol and *O*-desmethyltramadol changes, the nature of the substance and the total analgesic effect also change. Therefore, the analgesic effect cannot be predicted based on kinetic parameters. That is why it is not possible to calculate a dose adjustment in these cases.

PM + IM: the risk of reduced effectiveness of the therapy increases with these phenotypes. This is evidenced by the data from the literature. For this reason, the working group decides that action is needed for this gene-drug-interactions (yes/yes-interactions).
Literature shows that the *O*-desmethyltramadol/tramadol ratio is decreased in these phenotypes, so a dose adjustment cannot be calculated. If the analgesic effect is inadequate, it is recommended to try a dose increase. If this does not have the desired effect, it is recommended to select an alternative. Do not select codeine, as this is also metabolised by CYP2D6. Morphine is not metabolised by CYP2D6.

UM: Enhanced morphine-like side effects were observed in UMs in three cases. In a boy using tramadol after ambulatory adenotonsillectomy for obstructive sleep apnoea syndrome and in an adult with reduced renal function, these side effects were life-threatening. For this reason, the working group decides that action is needed for this gene-drug-interaction (yes/yes-interaction).
Four studies demonstrated an elevated plasma concentration of *O*-desmethyltramadol. Therefore, select an alternative. Do not select codeine, as this is also metabolised by CYP2D6. Morphine is not metabolised by CYP2D6. As the results for PMs, IMs and UMs indicate that (+)-*O*-desmethyltramadol plays a dominant role in both the analgesia and the side effects, a dose reduction is recommended if there are no alternatives. Only three of the studies that demonstrated an increase in AUC of *O*-desmethyltramadol stated this increase in comparison to EM. One of these (Stamer 2007, 8 UMs) used a median dose that cannot be used for the calculation of a weighted mean. The other two studies were Rauers 2010 (9 UM) and Saarikowski 2015 (4 UM). Based on the AUC of *O*-desmethyltramadol, the weighted mean of the dose adjustment calculated in these studies is a dose reduction to 38% of the standard dose (median 51%, range 17-85%). This was rounded off to 40% to be more achievable in clinical practice. This correlated well with the dose adjustment calculated based on the median AUCs in Stamer 2007 (reduction to 44% of the standard dose).

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.

Recommendation concerning pre-emptive genotyping, including justification of choices:

The Dutch Pharmacogenetics Working Group considers genotyping before starting tramadol to be potentially beneficial for drug safety and efficacy. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the Dutch Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 1 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points):
The reduced analgesic efficacy in patients with genetically reduced CYP2D6 activity (intermediate and poor metabolisers (IM and PM)) does not have a high clinical impact (severity code B corresponding to CTCAE grade 1). However, in patients with genetically enhanced CYP2D6 activity (ultra-rapid metabolisers (UM)), tramadol can cause serious and even life-threatening opioid toxicity (code E corresponding to CTCAE grade 4). This results in a score of 1 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for CTCAE grade 3 or 4).
Life-threatening opioid toxicity was only reported in two cases (a 5.5-year-old boy and a 66-year-old man). Toxicity code ≥ D (grade ≥ 3) was not reported in studies. This results in a score of 0 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 does not mention any CYP2D6 geno- or phenotype and the drug label from the USA states that individuals who are UM should not use tramadol, but does not mention this in the contra-indication section. Neither drug label recommends pre-emptive genotyping. The Dutch drug label results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the drug label (only points for at least one genotype/phenotype mentioned in the drug label).

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.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1
Seripa D et al.
Role of CYP2D6 polymorphisms in the outcome of postoperative pain treatment.
Pain Med 2015;16:2012-23.
PubMed PMID: 25989235.</td><td>3</td><td>90 patients received patient controlled intravenous analgesia with a maximum total dose of 200-400 mg tramadol and 320-640 mg ketoprofen after abdominal or thoracic surgery. Patients predicted to have severe post-operative pain received in addition a maximum total dose of 20 mg morphine. All patients received a maximum total dose of 20-40 mg metoclopramide and 100-200 mg ranitidine. Premedication was midazolam, diazepam, or no drug. Two patients received idrossizine to prevent allergic reactions. Anaesthesia was induced with propofol and remifentanil or fentanyl and maintained with the same drugs or with sevoflurane and remifentanil or fentanyl.
Pain was measured with the 10-point Numeric Rating Scale, sedation with the 6-point Ramsay Sedation Scale (RSS). Relevant co-medication was excluded.
The number of patients in this study resulted in 80% power to detect differences between the CYP2D6 phenotypes in the change of sedation between waking up and 24 hours later.

Genotyping:
- 55x EM
- 26x IM
- 3x PM
- 6x (UM + gene dose ≥ 2) (2x UM, 3x gene dose ≥ 2 (*4/*1xN), 1x gene dose ≥ 2.5 (*41/*1xN))

Results:<table><tr><td colspan="5">Results in comparison with EM:</td></tr><tr><td></td><td>PM</td><td>IM</td><td>UM +</td><td>value</td></tr></table></td><td>Authors' conclusion: 'In respect to the normal CYP2D6 phenotype, our results suggested that slowly metabolizers (IMs and PMs) might have a major sedation, whereas more rapid metabolizers (UM) a minor sedation, in the early time after surgery. A minor role of CYP2D6 phenotype in postoperative analgesia may be suggested.'</td></tr>
</table>

<table>
<tr>
<td>ref. 1, continuation</td>
<td>IM: B
PM: AA
UM: AA</td>
<td>
<table>
<tr><td></td><td></td><td></td><td>gene dose ≥ 2</td><td>for EM</td></tr>
<tr><td>vomiting</td><td>x 0</td><td>x 0</td><td>x 0</td><td>24% of patients</td></tr>
<tr><td></td><td colspan="3">S for the trend PM versus IM versus EM versus (UM + gene dose ≥ 2)</td><td></td></tr>
<tr><td>sedation 0.5 hour after waking up</td><td>x 1.36 (NS, trend, p = 0.091)</td><td>x 1.19 (S)</td><td>x 0.77 (NS, trend, p = 0.091)</td><td>RSS-score = 1.29</td></tr>
<tr><td></td><td colspan="3">S for the trend PM versus IM versus EM versus (UM + gene dose ≥ 2)</td><td></td></tr>
<tr><td>sedation at the time of, and 2, 6, 12, and 24 hours after waking up</td><td colspan="3">NS</td><td></td></tr>
<tr><td></td><td colspan="4">The timing of the CYP2D6 effect suggests that it is more likely to be an effect on recovery of sedation after anaesthesia than an effect on sedation by post-operative analgesia with tramadol.</td></tr>
<tr><td>pain at the time of, and 0.5, 2, 6, 12, and 24 hours after waking up</td><td colspan="3">NS</td><td></td></tr>
<tr><td>decrease in pain scores over time</td><td colspan="3">NS</td><td></td></tr>
</table>

NOTE: Genotyping was performed for *2 to *10, *12, *14, *17, *29, *41 and gene duplication (with identification of the duplicated allele).
</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Dong H et al.
Effect of the CYP2D6 gene polymorphism on postoperative analgesia of tramadol in Han nationality nephrectomy patients.
Eur J Clin Pharmacol 2015;71:681-6.
PubMed PMID: 25948472.</td>
<td>4

IM: B</td>
<td>111 patients received patient controlled intravenous analgesia with 15 mg tramadol per dose during 3 days after elective nephrectomy. About 30 minutes before termination of surgery, patients received an intravenous loading dose of 100 mg tramadol and 1 mg granisetron. If analgesia was insufficient, 50 mg intravenous tramadol was given as rescue mediation. Anaesthesia was induced with propofol and fentanyl and maintained with isoflurane and fentanyl.
Pain was measured with the 10-point visual analogue scale.
Relevant co-medication was excluded.

Genotyping:
- 33x gene dose 2
- 28x gene dose 1.5
- 50x IM

Results:
<table>
<tr><td colspan="4">Results in comparison with gene dose 2:</td></tr>
<tr><td></td><td>IM</td><td>gene dose 1.5</td><td>value for gene dose 2</td></tr>
<tr><td>pain score 2 hours after operation</td><td>x 1.5 (S)</td><td>x 1.0 (NS)</td><td>3.7</td></tr>
<tr><td>pain score 4, 24, 48 and 72 hours after operation</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td>total tramadol consumption 2</td><td>x 1.6 (S)</td><td>x 1.2 (NS)</td><td>44.8 mg</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘Different CYP2D6 *10 genotypes have an influence on the analgesic effect of tramadol in Han nationality patients after elective nephrectomy.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td></td>
<td>
<table>
<tr><td>hours after operation</td><td></td><td></td><td></td></tr>
<tr><td>total tramadol consumption 4, 24, 48 and 72 hours after operation</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td>patient controlled dosing 2 hours after operation</td><td>x 2.4 (S)</td><td>x 0.88 (NS)</td><td>0.8 times</td></tr>
<tr><td>patient controlled dosing 4 hours after operation</td><td>x 3.5 (S)</td><td>x 0.75 (NS)</td><td>0.4 times</td></tr>
<tr><td>patient controlled dosing 24, 48 and 72 hours after operation</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td>nausea and vomiting</td><td>NS</td><td>NS</td><td></td></tr>
</table>
NOTE: Genotyping was performed for *10. This is the most important gene variant in this Chinese patientgroup.
</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Orliaguet G et al.
A case of respiratory depression in a child with ultrarapid CYP-2D6 metabolism after tramadol.
Pediatrics 2015;135:e753-5.
PubMed PMID: 25647677.</td>
<td>2

UM: E</td>
<td>A 5.5-year-old boy of 21.0 kg became comatose with pinpoint pupils, minimal respiratory effort, frequent episodes of apnoea, and an oxygen saturation of 48%, on the morning after an oral dose of 20 mg tramadol (0.95 mg/kg). He took the dose 14 hours after ambulatory adenotonsillectomy under general anaesthesia for obstructive sleep apnoea syndrome. Non-invasive ventilation and three doses of 0.5 mg intravenous naloxone normalized consciousness, pupils, and respiration within minutes. He was discharged from hospital the next day.
There was no evidence of renal impairment. He was CYP2D6 UM (*2x2/*2). The urinary metabolic ratio O-desmethyltramadol/tramadol was significantly increased (0.63).</td>
<td>Authors' conclusion: 'Tramadol may be associated with a risk of respiratory depression after ambulatory tonsillectomy in children with ultrarapid CYP2D6 metabolism.'</td>
</tr>
<tr>
<td>ref. 4
Saarikoski T et al.
Effects of terbinafine and itraconazole on the pharmacokinetics of orally administered tramadol.
Eur J Clin Pharmacol 2015;71:321-7.
PubMed PMID: 25560051.</td>
<td>3

UM: AA</td>
<td>12 healthy volunteers received a single oral dose of 50 mg tramadol. Relevant co-medication was excluded.

Genotyping:
- 8x EM+IM (6x EM, 2x IM)
- 4x UM

Results:
<table>
<tr><td colspan="2">UM versus EM+IM:</td></tr>
<tr><td>AUC O-desmethyltramadol</td><td>x 1.18 (NS)</td></tr>
<tr><td>AUC ratio O-desmethyltramadol/tramadol</td><td>x 1.68 (NS)</td></tr>
<tr><td>oral clearance tramadol</td><td>x 1.46 (NS)</td></tr>
<tr><td colspan="2">The authors indicate that the lack of statistical significance is due to the low number of subjects in each genotype group.</td></tr>
</table>
NOTE: Genotyping was performed for *3 to *6, *9, *10, *41 and gene duplication. These are the most important gene variants in this Finnish patientgroup.</td>
<td>Authors' conclusion: 'The mean M1 $AUC_{0-\infty}$ was 18% higher in ultrarapid compared to extensive metabolizers; however, the difference was not statistically significant due to the low number of subjects in each genotype group.'

AUC O-DT versus EM:
UM: 118%</td>
</tr>
<tr>
<td>ref. 5
Zhao Q et al.
A logistic equation to determine the validity of tramadol from related gene polymorphisms and psychological factors.</td>
<td>3</td>
<td>200 patients received 100 mg intramuscular tramadol once, when the pain score on a 100 mm visual analogue scale was > 40 mm after upper limb fracture internal fixation surgery. Tramadol effectiveness was defined as a decrease of the pain score on the visual analogue scale with > 30 mm within 6 hours of the tramadol dose.
Relevant co-medication was not excluded.
Only 3 patients had adverse drug reactions (1x somnoles-</td>
<td>Authors' conclusion: 'Binary logistic regression analyses showed that CYP-2D6 genotype and anxiety level contributes predominately to tramadol respon-</td>
</tr>
</table>

<table>
<tr>
<td>Pharmacogenomics 2014;15:487-95.
PubMed PMID: 24624916.

ref. 5, continuation</td>
<td>IM: B</td>
<td>cence and 2x nausea/vomiting).

Genotyping:
- 58x gene dose 2
- 80x gene dose 1.5
- 62x IM

Results:
<table>
<tr><td colspan="4">Results in comparison with gene dose 2:</td></tr>
<tr><td></td><td>IM</td><td>gene dose 1.5</td><td>value for gene dose 2</td></tr>
<tr><td rowspan="3">% of patients in which tramadol was effective</td><td>x 0.35</td><td>x 0.73</td><td>83%</td></tr>
<tr><td colspan="3">S for the trend IM versus (gene dose 1.5) versus (gene dose 2)</td></tr>
<tr><td colspan="3">A binary logistic regression model showed that the CYP2D6 genotype was an independent predictive factor, but anxiety had a larger effect.</td></tr>
</table>

NOTE: Genotyping was performed for *10. This is the most important gene variant in this Chinese patientgroup.</td>
<td>ses, while p-gp genotype comes second. These findings indicate that poor tramadol responsiveness depends on both genetic and nongenetic factors and may be improved by lower anxiety levels and by genotyping for CYP2D6 *10 and p-gp 3435.’</td>
</tr>
<tr>
<td>ref. 6
Matouskova O et al. Pupillometry in healthy volunteers as a biomarker of tramadol efficacy.
J Clin Pharm Ther 2011;36:513-7.
PubMed PMID: 21729116.</td>
<td>3

IM: A
PM: A</td>
<td>69 healthy volunteers received a single oral dose of tramadol 0.7 mg/kg. The pupil response was measured 2 hours after intake as a measure of the pharmacological effect of tramadol. Noradrenalin re-uptake inhibitors such as tramadol dilate the pupils, opioids such as O-desmethyltramadol constrict the pupils. Co-medication was excluded.

Genotyping:
- 34x EM (*1/*1)
- 29x IM (*1/*4)
- 6x PM (*4/*4)

EM versus IM versus PM:
- decrease in the pupil constricting effect of tramadol with the number of *4 alleles (S for the trend and between the separate groups).
The decrease is observed both for the pupil size in the dark and for the minimum and final pupil size following a flash of light.
- tramadol reduced the pupil size in 92% of the EM, 52% of the IM and 33% of the PM (S).
Tramadol increased the size of the pupil in some of the patients.

NOTE: Genotyping was performed for *3 to *6 and gene duplication.</td>
<td>Authors’ conclusion: ‘The pharmacodynamic effects of tramadol were easily detected using both static and dynamic pupil parameters. The pharmacodynamic profiles were markedly influenced by the CYP2D6 phenotype.’</td>
</tr>
<tr>
<td>ref. 7
Rauers NI et al. Antagonistic effects of ondansetron and tramadol? A randomized placebo and active drug controlled study.
J Pain 2010;11:1274-81.
PubMed PMID: 20488759.</td>
<td>3</td>
<td>179 patients received intravenous ondansetron 4 mg (n=60), metoclopramide 10 mg (n=59) or placebo (n=60) after abdominal surgery, followed by intravenous tramadol 3 mg/kg (maximum of 250 mg) and metamizole 1 g. From 1.5 hours after administration, extra doses of tramadol 50 mg were given for high pain scores. Blood samples were collected at 0.5, 1.5 and 3 hours after administration. Relevant co-medication was not excluded. Existing medication was stopped on the day of the surgery, with the exception of anti-hypertensives and other medication for cardiac conditions.

Genotyping:
- 96x EM
- 56x IM</td>
<td>Authors’ conclusion: ‘Whereas plasma concentrations of (+)-O-demethyltramadol were significantly correlated to CYP2D6 genotype, no influence was detected for ondansetron.’</td>
</tr>
</table>

ref. 7, continuation	UM: A IM: AA PM: AA	- 18x PM - 9x UM UM versus EM: - increase in the AUC of (+)-O-desmethyl-tramadol by 490% (from 47.3 to 279.1 ng.hour/mL) (S) - the two UMs who received ondansetron did not develop any nausea and/or vomiting IM versus EM: - decrease in the AUC of (+)-O-desmethyl-tramadol by 20% (from 47.3 to 38.0 ng.hour/mL) (NS) PM versus EM: - decrease in the AUC of (+)-O-desmethyl-tramadol by 53% (from 47.3 to 22.2 ng.hour/mL) (NS) - the tramadol was stopped for 1 patient due to inadequate activity. This patient was a PM. NOTE: Genotyping was performed for *3 to *8, *10, *41 and gene duplication. The absence of PM and gene duplication corresponds to the low prevalence in Korean patients.	AUC (+)-*O*-DT versus EM: UM: 590% IM: 80% PM: 47%
ref. 8 Kim E et al. Adverse events in analgesic treatment with tramadol associated with CYP2D6 extensive-metaboliser and OPRM1 high-expression variants. Ann Rheum Dis 2010;69:1889-90. PubMed PMID: 20444752.	3 IM: AA#	53 osteoarthritis patients who developed nausea and/or vomiting during treatment with tramadol/paracetamol were compared to 101 patients who did not experience any side effects. Patients were treated with tablets of tramadol/paracetamol 37.5/325 mg for 14 days, or until side effects necessitated termination of the treatment. The dose was either 3 tablets per day or 1 tablet per day for 3 days, 2 tablets per day for 4 days and 3 tablets per day for 7 days. Tramadol/paracetamol was added to a stable dose of NSAIDs. Relevant co-medication was not excluded. The odds ratio was corrected for age, gender and genotype of the μ-opioid receptor. Genotyping: - 109x EM (gene doses 2 and 1.5) - 45x IM (gene doses 1 and 0.5) IM versus EM: - the risk of nausea and vomiting decreased by a factor of 3.4 (OR_{corr} = 0.29; 95% CI: 0.12 - 0.69; from 41% to 18% of the patients) (S) NOTE: Genotyping was performed for 36 polymorphisms and gene duplication. The absence of PM and gene duplication corresponds to the low prevalence in Korean patients.	Authors' conclusion: 'Although our findings need to be confirmed in larger populations to be used as pharmacogenetic prediction of tramadol toxicity, high-activity genotypes of CYP2D6 and a high-expression genotype of OPRM1 appear to confer high risk of nausea/vomiting in tramadol treatment.'
ref. 9 Stamer UM et al. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. Anesth Analg 2008;107:926-9.	2 UM: E	A 66-year-old man suffered respiratory depression and loss of consciousness 10.5 hours after tramadol therapy for postoperative pain (loading doses of tramadol 200 mg and 2x 50 mg i.v., followed by patient-controlled analgesia with tramadol 20 mg and metamizole 200 mg per dose i.v.). The man recovered following administration of naloxone. The maximum measured plasma concentrations of (+)-tramadol, (-)-tramadol, (+)-*O*-DT and (-)-*O*-DT were approximately 1000, 1000, 160 and 225 ng/mL respectively. The patient was UM (duplication of a wild type gene). In addition, he suffered from reduced renal function.	Authors' conclusion: 'Overall, this case confirms that CYP-2D6 duplication resulting in highly increased transformation to the active metabolite (+)ODT and concomitant renal impairment slowing (+)ODT clearance predispose patients to life-threatening opioid intoxication by tramadol's active metabolite.'

ref. 10 Halling J et al. CYP2D6 polymorphism in relation to tramadol metabolism: a study of faroese patients. Ther Drug Monit 2008;30:271-5.	3 PM: A	86 patients, 40x *1/*1, 34x *1/*4, 1x *1/*3, 1x *1/*6, 1x *1/*9, 1x *4/*9 and 8x *4/*4, who used tramadol 50-450 mg/day (median 100 mg/day), relevant co-medication not excluded; PM versus EM + IM + UM: - increase in the percentage of patients with a plasma concentration of (+)-*O*-DT lower than 5 nM. - no difference in median dose of tramadol. - no difference in the percentage of patients who also used other analgesia. NOTE: Alleles *3, *4, *6 and *9 were genotyped.	
ref. 11 Allegaert K et al. Postmenstrual age and CYP2D6 polymorphisms determine tramadol O-demethylation in critically ill neonates and infants. Pediatr Res 2008;63:674-9.	3 UM: A IM: A PM: A	41 seriously ill neonates or young children, distribution over the gene doses 0; 0.5; 1; 1.5; 2 and 3 not reported, loading dose of tramadol 2 mg/kg i.v., followed by continuous infusion of 5-8 mg/kg per 24 hours, co-medication unknown. - correlation gene dose with ratio *O*-DT/tramadol in plasma (S). Ratio is approximately 5-fold lower for gene dose 0.5 than for gene dose 2. - plasma concentrations *O*-DT lower than the detection limit (0.05 µg/mL): only found for PM (NS). The urine samples for PM also revealed a correlation between the gene dose and the ratio *O*-DT/tramadol (S). - the CYP2D6 activity and thus the effect of the gene dose increases with the post-menstrual age.	Authors' conclusion: 'Postmenstrual age and CYP2D6 polymorphisms determined O-demethylation activity in (pre)term neonates and young infants.'
ref. 12 Kirchheiner J et al. Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. J Clin Psychopharmacol 2008;28:78-83.	3 (UM + EM): A PM: A	22 volunteers, 11x UM + EM (gene duplication of *1, *2, *35 or *41 combined with *1, *2, *9, *10, *35 or *41), 3 PM (two alleles from the group *3, *4, *5 and *6) and 11x EM + IM (two alleles from the group *1, *2, *9, *10, *35 and *41), single dose of 100 mg tramadol, no co-medication, side effects were monitored over a period of 24 hours; (UM + EM) versus (EM + IM): - AUC (+)-*O*-DT increased by 14% (NS, from 501 to 572 mg.h/L). - AUC (-)-*O*-DT increased by 20% (NS, from 425 to 512 mg.h/L). - AUC (+)-tramadol decreased by 16% (NS, from 790 to 667 mg.h/L). - AUC (-)-tramadol decreased by 15% (NS, from 663 to 561 mg.h/L). - Increase in maximum plasma concentration (+)-*O*-DT by 27% (S, from 51 to 65 mg/L). - Increase in pain threshold and pain tolerance by 80% (NS, from 20 to 36 seconds) in a "cold pressor test". - Stronger increase in the pupil diameter (NS, from 1.4 to 2.2 mm). - Increase in the percentage of individuals with nausea (NS, from 9% to 46%). - Increase in the percentage of individuals vomiting (NS, from 0% to 9%). - Increase in the percentage of individuals with palpitations (NS, from 0% to 9%). PM versus (EM + IM): - AUC (+)-*O*-DT decreased by 83% (S, from 501 to 87 mg.h/L). - AUC (-)-*O*-DT decreased by 88% (S, from 425 to 51 mg.h/L). - AUC (+)-tramadol increased by 202% (S, from 790 to 2386 mg.h/L). - AUC (-)-tramadol increased by 257% (S, from 663 to 2370 mg.h/L).	Authors' conclusion: 'Pharmacokinetic differences between EMs and Ums were smaller than expected; nevertheless, UMs were more sensitive to tramadol than EMs.' AUC (+)-*O*-DT versus (EM + IM): PM: 17% (UM + EM): 114% AUC tramadol versus (EM + IM): PM: 327% (UM + EM): 85%

ref. 12, continuation		- No significant effect of tramadol on pain threshold and pain tolerance in a "cold pressor test". - Smaller increase in the pupil diameter (NS, from 1.4 to 1.0 mm). - 2 of the 4 individuals who experienced no sedation were PM (67% of the PM versus 9% of the (EM + UM + IM)). - Decrease in the percentage of individuals with headache (NS, from 45% to 0%). - Decrease in the percentage of individuals with nausea (NS, from 9% to 0%).	
ref. 13 Stamer UM et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007;82:41-7.	3 (PM + IM): B (IM + EM): A UM: A	174 patients, 18x PM + IM (2x *3/*5, 1x *3/*4, 14x *4/*4, 1x *4/*4/*41), 85x IM + EM (out of a group of 93: 50x (*1/*3, *1/*4, *1/*5, *1/*6 or *1/*4xN), 2x *10/*41, 1x *45/*45 or *45/*46, 6x (*3/*41, *4/*41, *6/*10 or *6/*41), 1x *1/*1 with unknown SNP, 31x (*1/*10 or *1/*41), 2x *1/*41xN), 62x EM (*1/*1), 8x UM (*1/*1xN), tramadol 3 mg/kg plus metamizole 1 g i.v., followed by 0-2 doses of tramadol 50 mg i.v. and patient-controlled analgesia with tramadol 20 mg and metamizole 200 mg per dose i.v. for post-operative analgesia, relevant co-medication not excluded. Pharmacokinetics were determined before administration of the 50 mg tramadol doses. Patients were monitored for 48 hours. (PM + IM) versus EM: - Decrease in median AUC (+)-*O*-DT by 100% (S, from 66.5 to 0 ng.h/mL). Plasma concentration of (+)-*O*-DT was below the detection limit of 2 ng/mL for 83% of the PMs. - Decrease in median AUC (-)-*O*-DT (S). - Comparison to EM without relevant co-medication: decrease in median AUC (+)-*O*-DT by 100% (S, from 88.7 to 0 ng.h/mL). - Increase in the percentage of patients that required rescue medication with piritramide by a factor of approximately 3.3 (S, from approximately 17% to 56%). - Increase in the percentage of patients with non-response after 48 hours by a factor of approximately 4.8 (S, from approximately 17% to 81%). - Increase in the cumulative dose of analgesics after 24 and 48 hours (S). (IM + EM) versus EM: - Decrease in the median AUC (+)-*O*-DT by 42% (NS, from 66.5 to 38.6 ng.h/mL). - Decrease in the median AUC (-)-*O*-DT (NS). - Sub-group without co-medication: Decrease in median AUC (+)-*O*-DT by 50% (S, from 88.7 to 44.1 ng.h/mL). UM versus EM: - Increase in the median AUC (+)-*O*-DT by 125% (NS, from 66.5 to 149.7 ng.h/mL). - Increase in the median AUC (-)-*O*-DT (NS). - Sub-group without co-medication (6 UM and 47 EM): increase in the median AUC (+)-*O*-DT by 125% (S, from 88.7 to 200.0 ng.h/mL).	Authors' conclusion: 'CYP2D6 genotype determined concentrations of O-desmethyltramadol enantiomers and influenced efficacy of tramadol treatment. Non-response rates to pain medication increased fourfold in PM and thus this genotype was associated with poor efficacy of tramadol analgesia.' Median AUC (+)-*O*-DT versus EM (without co-medication): (PM + IM): 0% (IM + EM): 50% UM: 225%
ref. 14 García-Quetglas E et al. Pharmacokinetics of tramadol enantiomers and their respective phase I metabolites in relation to CYP2D6	3 PM: A	24 volunteers, 5x PM and 11x EM# (phenotyped with tramadol), single dose of 100 mg tramadol, no co-medication, study duration 48 hours. Very low detection limit (0.5 ng/mL), meaning that (+)-*O*-DT can be measured in the plasma of all PMs. PM versus EM#: - Decrease in median AUC (+)-*O*-DT by 77% (S, from 0.325 to 0.075 ng.h/mL).	Authors' conclusion: 'The polymorphic CYP2D6 appears to be a major enzyme involved in the metabolism of tramadol enantiomers.'

phenotype. Pharmacol Res 2007;55:122-30. **ref. 14, continuation**		- Increase in the median AUC (-)-O-DT by 12% (NS, from 0.363 to 0.406 ng.h/mL). - AUC (+)-tramadol increased by 123% (S, from 0.898 to 2.002 mg.h/L). - AUC (-)-tramadol increased by 99% (S, from 0.717 to 1.427 mg.h/L). - Increase in the difference between C_{max} of (+)-*O*-DT and the average plasma concentration at which patients in a trial with patient-controlled analgesia administered themselves a new dose (33 ± 15 ng/mL) (decrease in C_{max} from 28 to 5 ng/mL (S)). - Decrease in the percentage of patients with side effects by 100% (S, from 47% to 0%). - Decrease in the percentage of patients with an increase in the plasma concentration of epinephrine by 100% (S, from 47% to 0%; increase only in the patients with side effects). NOTE: genotype unknown. It is not possible to distinguish between EM, IM and UM based on phenotyping. EM# is therefore equal to EM + IM + UM.	AUC (+)-*O*-DT versus EM#: PM: 23% AUC tramadol versus EM#: PM: 212%
ref. 15 Slanar O et al. Miotic action of tramadol is determined by CYP2D6 genotype. Physiol Res 2007;56:129-36.	3 PM: A IM: AA	21 volunteers, 7x PM (5x *4/*4, 1x *3/*3, 1x *3/*4), 7x IM (5x *1/*4, 2x *1/*3), 7x EM (*1/*1), single dose of 100 mg tramadol retard, no co-medication; PM versus EM: - Decrease in $AUC_{0\text{-}24h}$ *O*-DT by 68% (S, from 2,382 to 768 nmol.h/L). - Increase in $AUC_{0\text{-}24h}$ tramadol by 132% (S, from 4,986 to 11,544 nmol.h/L). - Decrease in the "area under the pupillary response-time curve" $AUD_{0\text{-}12h}$ by 78% (S, from 12.14 to 2.64 mm.h). IM versus EM: - Increase in the $AUC_{0\text{-}24h}$ *O*-DT by 7% (NS, from 2,382 to 2,553 nmol.h/L). - Increase in the $AUC_{0\text{-}24h}$ tramadol by 49% (NS, from 4,986 to 7,408 nmol.h/L). - Decrease in the "area under the pupillary response-time curve" $AUD_{0\text{-}12h}$ by 40% (NS, from 12.14 to 7.3 mm.h).	Authors' conclusion: 'The observed opioid action of the drug in subjects of different CYP2D6 genotypes is a plausible explanation for the use of this drug in clinical practice. A dual mechanism of action, not only in EMs, but also in PMs, would provide a theoretical basis for the better efficacy of tramadol in PMs than should be expected from only the non-opioid effects of tramadol.' AUC *O*-DT versus EM: PM: 32% IM: 107% AUC tramadol versus EM: PM: 232% IM: 149%
ref. 16 Wang G et al. Effect of the CYP2D6*10 C188T polymorphism on postoperative tramadol analgesia in a Chinese population. Eur J Clin Pharmacol 2006;62:927-31.	4 IM: B	63 patients, 20x *10/*10, 26x *1/*10, 17x *1/*1, tramadol 100 mg i.v., followed by patient-controlled analgesia with tramadol 15 mg and metoclopramide 0.45 mg per dose i.v. for post-operative analgesia, relevant co-medication excluded. Rescue medication was tramadol 50 mg i.v. Patients were monitored for 48 hours. *10/*10 versus *1/*1: - Increase in the total consumption of tramadol after 4, 24 and 48 hours by 10.3%, 15.9% and 13.2% respectively (S). - No difference in pain scores.	Authors' conclusion: 'This study indicates that the CYP2D6*10 allele has significant impact on analgesia with tramadol in a Chinese population.'

ref. 16, continuation		- Increase in the percentage of patients who were not satisfied with the pain medication (NS, from 12% to 45%). - No difference in the incidence of side effects. *1/*10 versus *1/*1: - Increase in the total consumption of tramadol over 48 hours by 1% (NS). - No difference in pain scores and the percentage of patients who were not satisfied with the pain medication. - No difference in the incidence of side effects.	
ref. 17 Pedersen RS et al. Enantioselective pharmacokinetics of tramadol in CYP2D6 extensive and poor metabolizers. Eur J Clin Pharmacol 2006;62:513-21.	4 PM: A	16 volunteers, 8x PM (7x *4/*4, 1x *4/*6), 8x EM (*1/*1), received a single oral dose of 150 mg tramadol at 2-week intervals, tramadol 50 mg orally every 8 hours for 48 hours and tramadol 100 mg i.v., no co-medication; PM versus EM, 50 mg orally every 8 hours: - Decrease in median AUC_{0-8h} (+)-O-DT by 87% (S, from 0.6 to 0.08 µmol.h/L). Plasma concentration of (+)-*O*-DT was below the detection limit of 1 nmol/L for 14% of the PMs. - Decrease in median AUC_{0-8h} (-)-O-DT by 29% (S, from 0.7 to 0.5 µmol.h/L). - Increase in median AUC_{0-8h} (+)-tramadol by 64% (S, from 2.2 to 3.6 µmol.h/L). - Increase in median AUC_{0-8h} (-)-tramadol by 67% (S, from 1.5 to 2.5 µmol.h/L). - No difference in biological availability of (+)-tramadol or (-)-tramadol. Tramadol single oral dose of 150 mg or 100 mg i.v.: - Similar effect of CYP2D6 phenotype on the pharmacokinetics. NOTE: Alleles *3, *4, *6 and *9 were genotyped.	Authors' conclusion: 'The impact of CYP-2D6 phenotype on tramadol pharmacokinetics was similar after single oral, multiple oral and intravenous administration displaying significant pharmacokinetic differences between EMs and PMs.' AUC (+)-*O*-DT versus EM: PM: 13% AUC tramadol versus EM: PM: 165%
ref. 18 Enggaard TP et al. The analgesic effect of tramadol after intravenous injection in healthy volunteers in relation to CYP2D6. Anesth Analg 2006;102:146-50.	3 PM: B	20 volunteers, 10x PM and 10x EM# (phenotyped with sparteine), single dose of 100 mg tramadol i.v., co-medication unknown except for alcohol or analgesics, pain measurement with "cold pressor test" and "electrical stimulation of calf nerve" 0-90 minutes after administration. *kinetic endpoints* - PM: plasma concentration of tramadol differs non-significantly versus EM. Plasma concentration of *O*-DT is reduced versus EM (S). (+)-*O*-DT below detection limit for all PMs, (-)-*O*-DT below detection limit for 6 PMs. - EM: Decrease in pain intensity with cold pressor test and AUC_{0-90} (+)-*O*-DT are correlated. *clinical endpoints* - PM: tramadol has no effect on pain measured with a cold pressor test in contrast to EM, it does result in an increase in the pain threshold with electrical stimulation of the calf nerve in contrast to EM. cold pressor test is opioid-sensitive; nerve stimulation is monoaminergic-sensitive. NOTE: genotype unknown. It is not possible to distinguish between EM, IM and UM based on phenotyping. EM# is therefore equal to EM + IM + UM.	Authors' conclusion: 'They also indicate that the monoaminergic mechanisms of the parent compound contribute to the action as there is some effect in poor metabolizers.'
ref. 19 Fliegert F et al. The effects of trama-	3	26 volunteers, 6x PM and 20x EM# (half phenotyped with sparteine, the other half genotyped, but no distinction between EM, IM and UM), single dose of 100 mg tramadol,	Authors' conclusion: 'The EMs and PMs of CYP2D6 treated

dol on static and dynamic pupillometry in healthy subjects -- the relationship between pharmacodynamics, pharmacokinetics and CYP2D6 metaboliser status. Eur J Clin Pharmacol 2005;61:257-66. **ref. 19, continuation**	PM: AA	no relevant co-medication; PM versus EM#: - Decrease in AUC (+)-*O*-DT (NS). AUC was 364 ng.h/mL for EMs, whilst the plasma concentrations were below the detection limit of 2.6 ng/mL for PMs. - Decrease in median AUC (-)-O-DT by 37% (NS, from 382 to 240 ng.h/mL). - Increase in AUC (+)-tramadol by 68% (NS, from 1,442 to 2,426 ng.h/mL). - Increase in AUC (-)-tramadol by 55% (NS, from 1,125 to 1,742 ng.h/mL). - Reduced decrease in the pupil diameter compared to placebo (S, from 0.8 mm to 0 mm). - Decrease in the average incidence of 5 side effects (NS, from 29% to 20%). NOTE: It is not possible to distinguish between EM, IM and UM based on phenotyping. EM# is therefore equal to EM + IM + UM.	with tramadol behaved differently in static and dynamic pupillometry. In EMs, the pupillometric response was mainly driven by the (+)-M1, which comprises the µ action component of tramadol; whereas, in PMs, the non-µ component appears to play an important role.' AUC tramadol versus EM#: PM: 162%
ref. 20 Borlak J et al. A rapid and simple CYP2D6 genotyping assay: case study with the analgetic tramadol. Metabolism 2003;52:1439-43.	3 PM: A IM: AA	24 volunteers, 6x PM (*3/*3, *3/*4, *4/*4), 7x IM (*1/*3 or *1/*4) and 11x EM (*1/*1), 2x 100 mg tramadol, on at least 5 consecutive days, no co-medication; - PM: increase in AUC tramadol from 2,143 to 3,941 ng/mL·hr versus EM (S by 84%), decrease in AUC DT from 843 to 300 ng/mL·hr (S by 64%). - IM: increase in AUC tramadol from 2,143 to 2,461 ng/mL·hr versus EM (NS by 15%), increase in AUC DT from 843 to 875 ng/mL·hr (NS by 4%).	AUC DT versus EM: PM: 36% IM: 104% AUC tramadol versus EM: PM: 184% IM: 115%
ref. 21 Stamer UM et al. Impact of CYP2D6 genotype on postoperative tramadol analgesia. Pain 2003;105:231-8.	3 PM: B	300 post-operative patients, 35x PM (1x *3/*5, 20x *4/*4, 1x *5/*5, 7x *6/*6, 2x *4/*5, 4x *6/*4), 98x IM (5x *1/*3, 81x *1/*1, 8x *1/*5, 2x *1/*6, 2x *1/*4 duplication), 158x EM (*1/*1), 9x duplication, with data for 271 patients, following titration of an individual loading dose of patient-controlled analgesia with tramadol 20 mg/mL, metamizole and metoclopramide as co-medication; - PM: number of non-responders is elevated compared to EM + IM (46.7% versus 21.6%, S). More rescue medication required in recovery (43.3 versus 21.6%, S). Tramadol loading dose was elevated by 33.3% compared to EM + IM (S). Tramadol dose during PCA was elevated by 26% (NS). Response = no rescue medication required + interview revealed that patient was satisfied with medication.	
ref. 22 Gan SH et al. Correlation of tramadol pharmacokinetics and CYP2D6*10 genotype in Malaysian subjects. J Pharm Biomed Anal 2002;30:189-195.	3 IM: A	30 orthopaedic patients, 2x *1/*1, 11x *1/*10 or *1/*9, 5x *1/*4 or *1/*5, 6x *10/*10 or *10/*17 and 5x *4/*10 or *5/*10, single dose of 100 mg tramadol i.v., co-medication unknown; - *4/*10 and *5/*10: increase in the AUC versus *1/*1 from 3,501 to 8,726 ng/mL·h (NS by 150%), decrease in Cl from 25.3 to 10.4 mL/min (S by 59%), increase in t½ from 6.6 to 21.6 hours. - *10/*10 and *10/*17: increase in the AUC versus *1/*1 from 3,501 to 6,710 ng/mL·h (NS by 92%), decrease in Cl from 25.3 to 14.3 mL/min (S by 44%), increase in t½ from 6.6 to 8.5 hours. - *1/*4 and *1/*5: increase in the AUC versus *1/*1 from 3,501 to 5,472 ng/mL·h (NS by 56%), decrease in Cl from 25.3 to 16.6 mL/min (S by 34%), increase in t½ from 6.6 to 7.5 hours. - *1/*10 and *1/*9: increase in the AUC versus *1/*1 from	AUC tramadol versus EM (*1/*1+*1/*10+ *1/*9): IM: 148%

ref. 22, continuation		3,501 to 4,909 ng/mL·h (NS by 42%), decrease in Cl from 25.3 to 20.4 mL/min (S by 19%), increase in t½ from 6.6 to 7.4 hours. N.B.: degree of pain varied per type of surgery.	
ref. 23 Abdel-Rahman SM et al. Concordance between tramadol and dextromethorphan parent/metabolite ratios: the influence of CYP2D6 and non-CYP2D6 pathways on biotransformation. J Clin Pharmacol 2002;42:24-9.	3 PM+IM: AA	26 volunteers (7-16 years), 12x genotyped (screened for *2 to *12, *15, *17, *18 and *29) and phenotyped (dextromethorphan), all (12x) EM, single body weight-adjusted dose of tramadol, no CYP inhibitors or inductors as co-medication; - less DT is formed with 1 functional allele than with 2 functional alleles, the C_{max} for tramadol does not differ between both groups. More *N*-DT is formed. NOTE: genotyping was performed, but the results are not shown	
ref. 24 Gleason PP et al. Debilitating reaction following the initial dose of tramadol. Ann Pharmacother 1997;31:1150-2.	1 UM: B	patient, 32 years old with shoulder pain, UM (MR-debrisoquine 0.23), single dose of 100 mg tramadol, no co-medication; 3 hours after intake of tramadol: ataxia, pupil dilation, stiffness in arms and legs, shaking and dysphoria, symptoms persisted for 4 hours.	
ref. 25 Paar WD et al. Polymorphic CYP2D6 mediates O-demethylation of the opioid analgesic tramadol. Eur J Clin Pharmacol 1997;53:235-9.	3 PM: A	104 volunteers, 80x phenotyped (sparteine), 9x PM and 71x EM#, single dose of 50 mg tramadol, no co-medication; - PM: increase in MR tramadol/*O*-DT versus EM (S) NOTE: genotype unknown. It is not possible to distinguish between EM, IM and UM based on phenotyping. EM# is therefore equal to EM + IM + UM.	
ref. 26 Poulsen L et al. The hypoalgesic effect of tramadol in relation to CYP2D6. Clin Pharmacol Ther 1996;60:636-44.	3 PM: B	27 volunteers, 12x PM and 15x EM# (phenotyped with sparteine), single dose of 2 mg/kg tramadol, no alcohol or analgesics, other co-medication unknown, pain measurement with "pressure pain test", stimulation of calf nerve and "cold pressor test" 2-10 hours after administration. *kinetic endpoints* - PM: increase in $AUC_{0\text{-}10hr}$ (+)-tramadol versus EM from 1,143 to 1,401 ng/mL·hr (S by 23%), increase in $AUC_{0\text{-}10hr}$ (-)-tramadol from 953 to 1,192 ng/mL·hr (S by 25%). AUC (+)-*O*-DT was around or below the detection limit, decrease in $AUC_{0\text{-}10hr}$ (-)-*O*-DT from 274 to 142 ng/mL·hr (S by 48%) *clinical endpoints* - PM: Significantly fewer side effects versus EM. Differed non-significantly from placebo. Comparable trend to EM for pain tests, but size of effect is smaller. - EM: a significant difference was found between tramadol and placebo for each of the three tests at both endpoints. Side effects occurred more often than with the placebo (S). For both phenotypes, there was no correlation between the magnitude of the response and the concentration of tramadol or *O*-DT. NOTE: genotype unknown. It is not possible to distinguish between EM, IM and UM based on phenotyping. EM# is	Authors' conclusion: 'Tramadol appeared to be a better analgesic in extensive metabolizers than in poor metabolizers. […] in extensive metabolizers, the analgesic effect of tramadol is due to both activation of monoaminergic antinociceptive pathways induced by the two enantiomers of tramadol and the μ-opioid receptor interaction of (+)-*O*-desmethyl-tramadol, whereas in poor metabolizers, the analgesic effect appears to be predominantly due to the effect on monoaminergic pathways.' AUC DT versus

ref. 26, continuation		therefore equal to EM + IM + UM.	EM#: PM: 52% AUC tramadol versus EM#: PM: 124%
ref. 27 SmPC Ultram (tramadol) 29-08-17, USA.	0 UM: E PM: A	Boxed warning: *Ultra-rapid metabolism of tramadol and other risk factors for life-threatening respiratory depression in children* Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism. ULTRAM is 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 ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. Pharmacokinetics/special populations: Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population pharmacokinetic analysis of phase 1 studies with immediate release tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers”, while O-desmethyltramadol concentrations were 40% lower. Warning: *Ultra-rapid metabolism of tramadol and other risk factors for life-threatening respiratory depression in children* Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype, which can lead to increased exposure to an active metabolite. Based upon post-marketing reports with tramadol or with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death: • ULTRAM is contraindicated for all children younger than 12 years of age • ULTRAM is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy. • Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as post-operative 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 opioids 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 opioid over-	

ref. 27, continuation		dose. *Nursing Mothers* Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of the active metabolite O-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking ULTRAM could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with ULTRAM. *CYP2D6 Genetic Variability: ultra-rapid metabolizer* Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP-2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert tramadol into its active metabolite, O-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 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 ULTRAM. Adverse events: The following serious adverse reaction is described, or described in greater detail, in other sections: • Ultra-rapid metabolism of tramadol and other risk factors for life-threatening respiratory depression in children	

AA#: There is a significant effect, but this effect is positive rather than negative.

Risk group	IMs with CYP2D6 inhibitor

Comments:

- Studies in which only concentrations in urine were measured were not included in this risk analysis.
  From 2009 onwards, kinetic studies were only included if the plasma concentration of O-desmethyltramadol was determined for UM and EM. Other kinetic studies do not contribute sufficiently to the evidence.
  For the same reason, a clinical study in which three groups of EM (*1/*1, *1/*2 and *2/*2) were compared to each other was not included.
  From 2012 onwards, kinetic studies without data on UM versus EM and studies on clinical effects in healthy volunteers were not included, because they did not contribute sufficiently to the evidence. Only for UM is a dose adjustment recommended. In addition, contrary to in healthy volunteers, tramadol is usually titrated and usually not the only analgesic drug in patients. A later version of Stamer 2007 was not included in the risk analysis, because it did not contribute sufficiently to the evidence.
- Algorithm:
  Zhao Q et al. A logistic equation to determine the validity of tramadol from related gene polymorphisms and psychological factors. Pharmacogenomics 2014;15:487-95. PubMed PMID: 24624916.
  The authors developed the following algorithm to predict tramadol response in Chinese patients:
  Logit (1) = 2.304 - 4.841x(mild anxiety) - 23.709x(moderate anxiety) + 2.823x(p-gp 3435CT) + 5.737x(p-gp 3435 TT) - 1.586x(CYP2D6 *1/*10) - 4.542x(CYP2D6 *10/*10).
  The cut-off value was 0.5 ($p > 0.5$ is higher probability of being effective, $p < 0.5$ is higher probability of being non-effective). Tramadol effectiveness was defined as a decrease of the pain score on the visual analogue scale with > 30 mm within 6 hours after 100 mg intramuscular tramadol once. Tramadol was given when the pain score on a

100 mm visual analogue scale was > 40 mm after upper limb fracture internal fixation surgery.
The algorithm was developed based on 200 patients and validated in an independent sample of 50 patients.
Relevant co-medication was not excluded. Only 3 patients had adverse drug reactions (1x somnolescence and 2x nausea/vomiting).
The positive predictive value in the large cohort was 90% and in the validation cohort 86%. The algorithm may be better in predicting non-response than in predicting response.

- Existing guidelines:
  - 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 does not have a guideline for tramadol, but the guideline for codeine contains also information on tramadol. 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).
    CPIC indicates that CYP2D6 poor metabolisers have been shown to have much lower median plasma areas under the concentration-time curve for (+)-O-desmethyltramadol, the metabolite responsible for opioid receptor-mediated analgesia, after a dose of tramadol as compared with extensive metabolizers (Stamer 2007). In addition, several prospective clinical trials have shown that, as compared with CYP2D6 extensive metabolisers, poor metabolisers more often fail to exhibit analgesia in response to tramadol (Poulsen 1996, Stamer 2003 and Stamer 2007). Pharmacokinetic studies in ultra-rapid metabolisers showed higher peak plasma concentrations of (+)-O-desmethyltramadol after a dose of tramadol, in addition to greater analgesia, stronger miosis, and higher incidence of nausea as compared with extensive metabolisers (Kirchheiner 2008).
    Based on the data above, CPIC concludes that it is likely that tramadol may have reduced clinical efficacy in CYP2D6 poor metabolisers. Use of an analgesic other than the CYP2D6 substrates tramadol, hydrocodone, or oxycodone in poor metabolizers may be preferable. In addition, if the CYP2D6 substrate tramadol is selected as alternative therapy in patients with gene dose 0.5, therapy should be monitored closely due to the possibility of poor response.

Phenotype/ genotype group	**Considerations for alternative opioids (i.e. alternatives for codeine)**
UM + gene dose 2.5	Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[a]
Gene dose 0.5	Monitor tramadol use for response.
PM	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]

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

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

Date of literature search: 19 October 2017.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
Dutch Pharmacogenetics Working Group Decision	PM	4 B	yes	yes	20 November 2017
	IM	4 B	yes	yes	
	UM	3 E	yes	yes	

Mechanism:
Tramadol is metabolised by CYP2D6, CYP3A4 and by glucuronidation. Conversion by CYP2D6 results in formation of the active metabolite *O*-desmethyltramadol, which has a 300x higher affinity for the μ-opioid receptor than the mother substance. The (+)-enantiomer of *O*-desmethyltramadol is the active enantiomer. Tramadol itself has an analgesic effect through inhibition of the re-uptake of norepinephrine and serotonin.