CYP2D6: atomoxetine 1598/1599/1600

ADHD = attention deficit hyperactivity disorder, AUC = area under the concentration-time curve, AUEC = area under the time-effect curve, 95% CI = 95% confidence interval, Cl_{or} = oral clearance, C_{ss} = steady state plasma concentration, DBP = diastolic blood pressure, 4-HA = 4-hydroxyatomoxetine, IM = intermediate metaboliser (gene dose 0.25-1) (reduced CYP2D6 enzyme activity), MR = metabolic ratio, N-DA = N-desmethylatomoxetine, NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, OR = odds ratio, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), QT_c interval = the QT interval corrected for heart rate, S = significant, SBP = systolic blood pressure, SmPC = Summary of Product Characteristics, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (elevated 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 healthcare professional should consider the next best option.

Brief summary and justification of choices:
CYP2D6 converts atomoxetine to 4-hydroxyatomoxetine. This metabolite is equipotent to atomoxetine, but circulates in much lower concentrations in the plasma.
The plasma concentrations of atomoxetine in subjects with absent CYP2D6 activity (poor metabolisers, PM) are much higher and those in subjects with reduced CYP2D6 activity (intermediate metabolisers, IM) are higher than in subjects with normal CYP2D6 activity (normal metabolisers, NM), also when the dose is adjusted based on efficacy and side effects (Brown 2016 (11 IM and 4 PM), Michelson 2007 (237 PM from 14 studies including 4 registration studies), the SmPCs of atomoxetine (data on PM only), Jung 2020 (7 healthy IM), Kim 2018 (8 healthy IM), Byeon 2015 (18 healthy IM), Matsui 2012 (healthy, 9 IM, 11 PM), Cui 2007 (7 healthy IM), and Sauer 2003 (3 healthy PM)). However, this only results in a limited increase in side effects, probably due to the wide therapeutic range of atomoxetine (Brown 2016 (11 IM and 4 PM), Fijal 2015 (701 IM + 79 gene dose 1.25-1.5, 117 PM), ter Laak 2010 (10 patients with side effects, among whom 6 IM), Trzepacz 2008 (87 PM), Michelson 2007 (237 PM from 14 studies including 4 registration studies), the SmPCs of atomoxetine (data on PM only), Loghin 2013 (131 healthy PMs), Matsui 2012 (9 healthy IM), and Cui 2007 (7 healthy IM)). As a result, it is generally not necessary to reduce the dose for PM and IM to such an extent that the plasma concentrations become identical to those for NM.
Atomoxetine is not effective in some patients. There are indications that the percentage of patients for whom atomoxetine is not effective decreases with increasing plasma concentrations of atomoxetine. A higher plasma concentration can therefore also have a favourable effect.
As an increase in side effects was also found for IM and PM when the dose was adjusted based on efficacy and side effects, it was decided that a therapeutic recommendation is required for these gene-drug interactions (yes-yes-interactions).
Hardly any data have been published for patients with an elevated CYP2D6 activity (ultra-rapid metaboliser, UM). For 1 UM, a decrease in the AUC by approximately two thirds was found compared to the average for 7 NMs (Brown 2016). Due to the risk of reduced efficacy, it was decided that a therapeutic recommendation is also required for this gene-drug interaction (yes-yes-interaction).
An overview of the observed clinical and kinetic effects per phenotype is provided in the background information text of the gene-drug interactions in the KNMP Kennisbank. You may also have access to this background information text via your pharmacy or physician electronic decision support system. A substantiation of the therapeutic recommendation is provided below per phenotype.
Therapeutic recommendation per predicted phenotype (genotype group):

PM: The AUC is a factor 8-11 higher than for NM (Brown 2016 (4 PM), the SmPCs of atomoxetine, Matsui 2012 (healthy, 11 PM), and Sauer 2003 (3 healthy PM)). These changes are associated with a significantly more frequent occurrence of side effects, including insomnia, decreased appetite and weight loss, depression, tremor, etc. (Fijal 2015 (117 PM), Trzepacz 2008 (87 PM), Michelson 2007 (237 PM from 14 studies including 4 registration studies), the SmPCs of atomoxetine, and Loghin 2013 (131 healthy PMs)), although a small study did not find an effect (Brown 2016 (4 PM)). An increase in the side effects was also found with repeated doses (Fijal 2015 (117 adult PMs)) and with normal adjustment of the treatment (Michelson 2007 (237 paediatric PMs from 14 studies including 4 registration studies)). The latter study also found an increa-

sed efficacy for 30 PM from 4 registration studies, but Ramoz 2009 (19 paediatric PMs) and Trzepacz 2008 (87 paediatric PMs) did not.
The American Summary of Product Characteristics gives a dose recommendation for adjustment of the dose in PM or when used in combination with a CYP2D6 inhibitor: start with the standard initial dose, but only increase this dose if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. The KNMP Pharmacogenetics Working Group decided to adopt this dose recommendation. The KNMP Pharmacogenetics Working Group further decided to add, that, if the initial dose is not well tolerated, but does result in an improvement of symptoms, it should be determined whether efficacy can also be achieved at a lower dose.

IM: For IM, the AUC is a factor 2-3 higher (Brown 2016 (11 IM), Jung 2020 (7 healthy IM), Kim 2018 (8 healthy IM), Byeon 2015 (18 healthy IM), Matsui 2012 (9 healthy IM), and Cui 2007 (7 healthy IM)), but due to the wide therapeutic range of atomoxetine, this appears to have only a limited effect on the side effects (Brown 2016 (11 IM), Fijal 2015 (701 IM + 79 gene dose 1.25-1.5), Ter Laak 2010 (10 patients with side effects, among whom 6 IM), Matsui 2012 (9 healthy IM), and Cui 2007 (7 healthy IM)). One study involving adults found a limited increase in the number of patients with a dry mouth and sleep disorders for 701 IM + 79 patients with gene dose 1.25-1.5 (OR = 1.6 and 1.7) (Fijal 2015). Three small studies did not find a significant difference in side effects for IM (Brown 2016 (11 IM), Matsui 2012 (9 healthy IM), and Cui 2007 (7 healthy IM)). The study by Ter Laak 2010 found that 6 out of 10 patients who experienced side effects and/ or had a late response at a standard dose were IM. For the two IM who then received a reduced dose (to 1.14 mg/kg per day and 0.42 mg/kg per day), this resulted in conserved efficacy and a reduction of the side effects. For this reason, if side effects occur, the KNMP Pharmacogenetic Working Group recommends to check whether efficacy can also be achieved at a lower dose.

UM: No clinical data are available for UM. The KNMP Pharmacogenetics Working Group recommends to be alert to reduced efficacy as a precaution, due to the reduced plasma concentration of atomoxetine.

A possible non-stimulant alternative that is not metabolised by CYP2D6, is clonidine.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting atomoxetine to be potentially beneficial for the prevention of side effects and drug effectiveness. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the KNMP 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) (see also the clinical implication score tables at the end of this risk analysis):
No severe clinical effects were observed in users of atomoxetine with a variant phenotype. The maximum severity code was B corresponding to CTCAE grade 1. This results in a score of 0 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 (only points for CTCAE grade ≥ 3).
The lack of a severe clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3).
The Summary of Product Characteristics (SmPC) of atomoxetine mentions a higher incidence of adverse events in PM patients, but does not mention PM to be a contra-indication and does not recommend pre-emptive genotyping. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).

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

Source	Code	Effect	Comments
ref. 1 Jung EH et al. Effects of paroxetine on the pharmacokinetics of atomoxetine and its metabolites in different CYP2D6 genotypes. Arch Pharm Res 2020;43:1356-63.	3	26 healthy volunteers received a single dose of atomoxetine 20 mg. None of the volunteers had an adverse event. All volunteers were CYP2C19 NM (no *2, *3, and *17). All were asked to abstain from taking other medications, caffeine, grapefruit products, alcoholic beverages, and any products that can affect the results of the study, and smoking for at least 1 week before and during the study. Genotyping: - 10x gene dose 2 - 9x gene dose 1.25	Authors' conclusions: 'When atomoxetine was administered alone, C_{max}, AUC_{0-24} and CL/F of atomoxetine were significantly different among the three CYP2D6 genotype groups.'

<table>
<tr>
<td>PMID: 33245517.

ref. 1, continuation</td>
<td>IM: A</td>
<td>- 7x IM (gene dose 0.5)

Results:
<table>
<tr><td colspan="4">$AUC_{0\text{-}24h}$ compared to gene dose 2:</td></tr>
<tr><td></td><td>IM</td><td>gene dose 1.25</td><td>value for gene dose 2</td></tr>
<tr><td>atomoxetine</td><td>x 3.07 (S)</td><td>x 1.72 (S)</td><td>497.7 ng.h/mL</td></tr>
<tr><td>4-hydroxy-atomoxetine</td><td>x 1.23 (NS)</td><td>x 0.92 (NS)</td><td>10.8 ng.h/mL</td></tr>
</table>

NOTE: Genotyping was performed for *2, *5, *10, and gene duplication. These are the most important gene variants in this Korean population.</td>
<td>AUC atomoxetine compared to gene dose 2:
IM: 307%</td>
</tr>
<tr>
<td>ref. 2
Kim SH et al. Physiologically based pharmacokinetic modelling of atomoxetine with regard to CYP2D6 genotypes.
Sci Rep 2018;8:12405.
PMID: 30120390.</td>
<td>3

IM: A</td>
<td>19 healthy volunteers selected according to genotype received a single dose of atomoxetine 20 mg.
CYP2C19 PMs and use of any medications, alcohol, or caffeine for 10 days prior to or during the pharmacokinetic study were excluded.
The power of the study was at least 80%. The sample size was estimated to be sufficient to detect 100% greater AUC of atomoxetine among the two genotype groups.

Genotyping:
- 11x NM (gene dose 2)
- 8x IM (*10/*10)

Results:
<table>
<tr><td colspan="2">AUC of atomoxetine compared to NM (521.09 ng.h/mL):</td></tr>
<tr><td>IM (gene dose 0.5)</td><td>x 3.14 (S)</td></tr>
</table>

NOTE: Genotyping was performed for *2, *5, *10, and gene duplication. These are the most important gene variants in this Korean population.</td>
<td>Authors' conclusions: 'The C_{max}, $AUC_{0–24}$, AUC_{inf}, $t_{1/2}$, and CL/F were all significantly different between those with CYP2D6 *wt/*wt and CYP2D6 *10/*10 genotypes.'

AUC atomoxetine compared to gene dose 2:
IM: 314%</td>
</tr>
<tr>
<td>ref. 3
Brown JT et al. Single dose, CYP-2D6 genotype-stratified pharmacokinetic study of atomoxetine in children with ADHD.
Clin Pharmacol Ther 2016;99:642-50.
PubMed PMID: 26660002.</td>
<td>3

IM: A
PM: A</td>
<td>23 children with ADHD selected according to genotype received a single dose of atomoxetine 0.34-0.59 mg/kg.
Two patients were overweight and 8 were obese. CYP2D6 inhibiting co-medication was excluded.

Genotyping:
- 1x UM (gene dose 3)
- 7x NM
- 11x IM (7x gene dose 1, 1x gene dose 0.75, and 3x gene dose 0.5)
- 4x PM

Results:
<table>
<tr><td colspan="2">Dose-corrected and weight-corrected AUC of atomoxetine versus NM+UM (4.4 nmol.hour/mL per 0.5 mg/kg):</td></tr>
<tr><td>gene dose 0.75-1</td><td>x 1.3 (NS)</td></tr>
<tr><td>gene dose 0.5</td><td>x 3.7 (S)</td></tr>
<tr><td>PM</td><td>x 11.4 (S)</td></tr>
<tr><td colspan="2">Side effects:
There were no significant differences in side effects between the groups (NS). Side effects occurred in 10 of the 23 volunteers, with drowsiness occurring in 8 patients. Other side effects included palpitations and tachycardia (1 PM), a hot flush (1x gene dose 1 or 0.75), a feeling of light-headedness (1x gene dose 1 or 0.75) and dizziness, nausea and headache (1x gene dose 0.5).</td></tr>
</table>
</td>
<td>Authors' conclusions: 'Dose-corrected atomoxetine systemic exposure varied 29.6-fold across the study cohort, ranging from 4.4 µM*h in NM2s to 5.86 µM*h, 16.36 µM*h, and 50.26 µM*h in NM1s, IMs, and PMs, respectively (P<0.0001). Simulated steady state profiles at the maximum FDA-recommended dose suggest that most patients are unlikely to attain adequate atomoxetine exposures. These data support the need for individualized dosing strategies for more effective use of the medication.'

AUC atomoxetine compared to</td>
</tr>
</table>

ref. 3, continuation	UM: AA	Effect on heart rate and blood pressure: There were no significant differences in the effect on heart rate and blood pressure between the groups (NS). The increase in heart rate was comparable between the groups. An increase in the systolic blood pressure by > 20 mmHg occurred in 1 PM, 1x gene dose 1 or 0.75,and 1 NM. The concentration of 4-hydroxyatomoxetine was less than 1% of the concentration of atomoxetine. Dose-corrected and weight-corrected AUC of atomoxetine versus NM (approx. 4.8 nmol.hour/mL per 0.5 mg/kg): UM: approx. x 0.32 (NS) The dose-corrected and weight-corrected AUC of atomoxetine for NM was only included in the article as a figure and not as a number. Therefore, the precision of the values determined for NM and UM is low. The concentration of 4-hydroxyatomoxetine was less than 1% of the concentration of atomoxetine. The authors indicate that atomoxetine is not effective in 40% of the children (Newcorn 2009). Michelson 2007 estimated that the maximum improvement in ADHD symptoms occurred at an atomoxetine peak concentration of 800 ng/mL (approximately 3.1 nmol/mL). An almost maximum response can occur at concentrations above 400 ng/mL. In one study involving 294 patients, 87% did not achieve the limit of 800 ng/mL after six weeks at a dose of 1.2 mg/kg per day (Eli Lilly & Company, 2015). In this study, 39% of the patients with atomoxetine concentrations < 800 ng/mL experienced an adequate reduction in ADHD symptoms, whilst this figure rose to 55% for patients with concentrations > 800 ng/mL. In the PM group 88% achieved the limit of 800 ng/mL, whilst only 9% of NM achieved this limit. With simulation of multiple doses of the maximum recommended dose of 1.4 mg/kg per day with a maximum of 100 mg/day for the 23 patients in this study, only the 4 PM patients, 2 patients with gene dose 0.5 and 2 patients with gene dose 1 achieved the limit value of 800 ng/mL. On average, the PM achieved a peak concentration of 2,360 ng/mL (9.1 nmol/mL), with the concentration being higher than 800 ng/mL approximately 82% of the time. NOTE: Genotyping was performed for *2 to *7, *9 to *12, *15, *17, *29, *31, *35, *36, *40-*42, *45/46, CYP2D6*13-like CYP2D7/2D6 hybrid genes and gene duplication.	NM+UM: gene dose 0.75-1: 130% gene dose 0.5: 370% IM: 200% PM: 1140% AUC atomoxetine compared to NM: UM: approx. 32%
ref. 4 Byeon JY et al. Effects of the CYP2D6*10 allele on the pharmacokinetics of atomoxetine and its metabolites. Arch Pharm Res 2015;38:2083-91. PubMed PMID: 26254792.	3	62 healthy volunteers received a single dose of atomoxetine. The dose was 40 mg for all 22 patients with gene dose 2. For patients with gene dose 1.5, the dose was 40 mg (n = 4), 30 mg (n = 9) or 16 mg (n = 9). For IM (gene dose 1), the dose was 40 mg (n = 6) or 12 mg (n = 12). Co-medication, alcohol and caffeinated drinks were excluded. Genotyping: - 22x gene dose 2 - 22x gene dose 1.25 - 18x IM (gene dose 0.5) Results: Dose-corrected and weight-corrected AUC of atomoxetine + 4-hydroxyatomoxetine versus gene dose	Authors' conclusions: 'The concentration of active moieties of atomoxetine (atomoxetine + 4-HAT) in the CYP2D6*10/*10 group was 3.32-fold higher than that in the CYP2D6*wt/*wt group.' AUC atomoxetine + 4-HA compared to

<table>
<tr>
<td>ref. 4, continuation</td>
<td>IM: A</td>
<td>
<table>
<tr><td colspan="2">2 (5.06 nmol.kg.hour/mL.mg):</td></tr>
<tr><td>IM</td><td>x 3.32 (S)</td></tr>
<tr><td>gene dose 1.25</td><td>x 1.32 (S)</td></tr>
<tr><td colspan="2">No side effects occurred in the study.</td></tr>
</table>

NOTE: Genotyping was performed for *2, *5, *10 and gene duplication. These are the most common polymorphisms in this Asian population group.
</td>
<td>gene dose 2:
IM: 332%</td>
</tr>
<tr>
<td>ref. 5
Fijal BA et al.
CYP2D6 predicted metabolizer status and safety in adult patients with attention-deficit hyperactivity disorder participating in a large placebo-controlled atomoxetine maintenance of response clinical trial.
J Clin Pharmacol 2015;55:1167-74.
PubMed PMID: 25919121.</td>
<td>3

IM: B
PM: B</td>
<td>A group of 1,936 adult ADHD patients started a 12-week course of treatment with atomoxetine (40 mg/day during weeks 1 and 2, followed by an increase to 80 mg/day, after 2-4 weeks at 80 mg/day the dose could be increased if necessary to 100 mg/day, no dose reduction in the last 4 weeks). Patients who did not complete the treatment (50% of all patients) were also analysed. Relevant co-medication was not excluded.
Side effects requiring treatment, that occurred in at least 5% of the patients in one of the genotype groups, were analysed. These included both new symptoms and a worsening of existing symptoms.
Only side effects and changes for which a significant effect or a trend (p < 0.1) was found were included in the risk analysis.

Genotyping:
- 67x UM
- 972x gene dose 2
- 780x IM + gene dose 1.25-1.5 (701x IM, 79x gene dose 1.25-1.5)
- 117x PM

Results:
<table>
<tr><td colspan="5">OR for side effects requiring treatment and average change in blood pressure, heart rate and weight:</td></tr>
<tr><td></td><td>IM versus NM/UM</td><td>PM versus NM/UM/IM</td><td>Value for NM/UM</td><td>Value for NM/UM/IM</td></tr>
<tr><td>Dry mouth</td><td>1.6 (S)</td><td>2.2 (S)</td><td>13.1%</td><td>15.9%</td></tr>
<tr><td>Urine retention</td><td>NS</td><td>9.1 (S)</td><td>0.6%</td><td>0.7%</td></tr>
<tr><td>Erectile dysfunction</td><td>NS</td><td>3.1 (S)</td><td>7.5%</td><td>7.2%</td></tr>
<tr><td>Decreased appetite</td><td>NS</td><td>2.0 (S)</td><td>13.1%</td><td>13.9%</td></tr>
<tr><td>Insomnia</td><td>NS</td><td>2.1 (S)</td><td>6.9%</td><td>7.8%</td></tr>
<tr><td>Sleep disorders</td><td>1.7 (S)</td><td>NS</td><td>2.5%</td><td>3.2%</td></tr>
<tr><td>Excessive sweating</td><td>NS</td><td>2.0 (S)</td><td>8.0%</td><td>8.2%</td></tr>
<tr><td>Nausea</td><td>NS</td><td>trend towards a reduction (p = 0.052)</td><td>27.7%</td><td>27.0%</td></tr>
<tr><td>Dizziness</td><td>NS</td><td>trend towards an increase (p = 0.085)</td><td>7.3%</td><td>8.1%</td></tr>
<tr><td>Constipation</td><td>NS</td><td>trend towards an increase</td><td>3.8%</td><td>4.0%</td></tr>
</table>
</td>
<td>Authors' conclusions: 'Common (> 5% frequency) treatment-emergent adverse events did not significantly differ between normal/ultrarapid and intermediate metabolizers (odds ratios were <2.0 or >0.5). Poor metabolizers had higher frequencies of dry mouth, erectile dysfunction, hyperhidrosis, insomnia, and urinary retention compared with the other metabolizer groups. There were no significant differences between normal/ultrarapid and intermediate metabolizers in changes from baseline in vital signs.'</td>
</tr>
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<td>ref. 5, continuation</td>
<td></td>
<td>
<table>
<tr><td></td><td></td><td>(p = 0.090)</td><td></td><td></td></tr>
<tr><td>Increased heart rate</td><td>NS</td><td>x 1.7 (S)</td><td>+ 5.6 beats/ min.</td><td>+ 5.8 beats/ min.</td></tr>
<tr><td>Increase in diastolic blood pressure</td><td>NS</td><td>x 2.2 (S)</td><td>+ 1.6 mm Hg</td><td>+ 1.7 mm Hg</td></tr>
<tr><td>Reduction in BMI</td><td>NS</td><td>trend (p = 0.050)</td><td>- 0.3 kg/ cm^2</td><td>- 0.3 kg/ cm^2</td></tr>
<tr><td>Reduction in body weight</td><td>NS</td><td>trend (p = 0.053)</td><td>- 0.9 kg</td><td>- 0.9 kg</td></tr>
<tr><td colspan="5">A calculation to determine the effect of addition of genotyping for *41 suggested that inclusion of genotyping for this allele would not have had any effect on the results.</td></tr>
<tr><td colspan="5">IMs were not overrepresented in the group of patients who did not finish the treatment.</td></tr>
<tr><td colspan="5">The average dose during the study was comparable for IM and NM/UM.</td></tr>
</table>

NOTE: Genotyping was performed for *3-*8, *10, *17 and gene duplication. These are the most common variant alleles in this mainly White population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Loghin C et al. Effects of atomoxetine on the QT interval in healthy CYP2D6 poor metabolizers. Br J Clin Pharmacol 2013;75:538-49. PubMed PMID: 22803597.</td>
<td>4

PM: A</td>
<td>131 healthy, male CYP2D6 PMs received four treatments in a cross-over study: atomoxetine 20 mg 2x daily, atomoxetine 60 mg 2x daily, placebo or a single dose of moxifloxacin 400 mg. Atomoxetine 20 mg 2x daily and placebo were given for a period of 7 days. Atomoxetine 60 mg 2x daily consisted of atomoxetine 20 mg 2x daily on day 1, atomoxetine 40 mg 2x daily on day 2 and atomoxetine 60 mg 2x daily on days 3-7. The maximum dose of atomoxetine in the Netherlands is 100 mg/day.
9 PM terminated the study prematurely. Data were determined for 126 patients (placebo and atomoxetine 20 mg 2x daily) and for 125 patients (atomoxetine 60 mg 2x daily).
Co-medication, alcohol and food or drinks containing xanthines were excluded.
The most important correction method for the QT interval was a correction method based on a repeated-measures model (Dmitrienko 2003). They performed 5 QT measurements per day for atomoxetine and placebo, at various time points after taking the morning dose. Data were also calculated for the time point with the peak concentration of atomoxetine (C_{max}, median 2 hours after taking the dose, but not the same for all patients).
The effect was considered clinically significant if the upper limit of the two-sided 90% confidence interval (equivalent to the upper limit of the one-sided 95% confidence interval) of the QT_c variation in comparison to the placebo was greater than 10 msec.

Results:
<table>
<tr><td colspan="6">Least-squares mean ΔQT_c between atomoxetine and placebo (ΔQT_c) and two-sided 90% confidence interval (90% CI) at various time points after taking the morning dose and at the time point of C_{max}:</td></tr>
<tr><td rowspan="2">Correction method</td><td rowspan="2">time (hour)</td><td colspan="2">atomoxetine 20 mg 2x daily</td><td colspan="2">atomoxetine 60 mg 2x daily</td></tr>
<tr><td>ΔQT_c</td><td>90% CI</td><td>ΔQT_c</td><td>90% CI</td></tr>
<tr><td>Model-</td><td>1</td><td>0.0</td><td>-1.7 - 1.7</td><td>2.3</td><td>0.6 - 4.0</td></tr>
</table>
</td>
<td>Authors' conclusions: 'Atomoxetine was not associated with a clinically significant change in QT_c. However, a statistically significant increase in QT_c was associated with increasing plasma concentrations.'</td>
</tr>
</table>

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<tr>
<td>ref. 6, continuation</td>
<td></td>
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<table>
<tr><td>based QT_c</td><td>2</td><td>0.5</td><td>-1.2 - 2.2</td><td>4.2</td><td>2.5 - 6.0</td></tr>
<tr><td></td><td>4</td><td>-1.5</td><td>-3.2 - 0.2</td><td>3.8</td><td>2.1 - 5.6</td></tr>
<tr><td></td><td>6</td><td>-2.0</td><td>-3.7 - -0.3</td><td>1.4</td><td>-0.3 - 3.1</td></tr>
<tr><td></td><td>12</td><td>-1.1</td><td>-2.7 - 0.6</td><td>1.9</td><td>0.2 - 3.6</td></tr>
<tr><td></td><td>C_{max}</td><td>-0.8</td><td>-2.6 - 1.1</td><td>2.7</td><td>0.7 - 4.7</td></tr>
<tr><td>QT_cF (Fridericia's QT correction)</td><td>1</td><td>-0.1</td><td>-1.7 - 1.5</td><td>2.7</td><td>1.1 - 4.3</td></tr>
<tr><td></td><td>2</td><td>0.3</td><td>-1.3 - 1.9</td><td>4.6</td><td>3.0 - 6.2</td></tr>
<tr><td></td><td>4</td><td>-1.7</td><td>-3.3 - -0.1</td><td>4.4</td><td>2.8 - 6.0</td></tr>
<tr><td></td><td>6</td><td>-1.9</td><td>-3.5 - -0.3</td><td>2.2</td><td>0.6 - 3.8</td></tr>
<tr><td></td><td>12</td><td>-1.0</td><td>-2.6 - 0.6</td><td>2.6</td><td>1.0 - 4.2</td></tr>
<tr><td></td><td>C_{max}</td><td>0.1</td><td>-1.4 - 1.6</td><td>4.4</td><td>2.9 - 5.9</td></tr>
<tr><td>QT_cI (individual QT correction)</td><td>1</td><td>-1.6</td><td>-3.3 - 0.1</td><td>0.6</td><td>-1.1 - 2.3</td></tr>
<tr><td></td><td>2</td><td>-0.9</td><td>-2.6 - 0.9</td><td>2.4</td><td>0.7 - 4.1</td></tr>
<tr><td></td><td>4</td><td>-3.2</td><td>-4.9 - -1.5</td><td>1.7</td><td>0.0 - 3.4</td></tr>
<tr><td></td><td>6</td><td>-2.9</td><td>-4.6 - -1.2</td><td>0.0</td><td>-1.7 - 1.7</td></tr>
<tr><td></td><td>12</td><td>-2.2</td><td>-3.9 - -0.5</td><td>0.7</td><td>-1.1 - 2.4</td></tr>
<tr><td></td><td>C_{max}</td><td>-1.0</td><td>-2.6 - 0.5</td><td>2.4</td><td>0.9 - 4.0</td></tr>
</table>
ΔQT_c was higher and more often significant for atomoxetine 60 mg 2x daily than for 20 mg 2x daily, but remained low (< 10 msec).

Individual QT_c values:
There were no individuals with QT_cF or QT_cI > 500 msec at any time point.
There were also no individuals at any time point with an elongation of the QT_cF of QT_cI > 60 msec compared to before the treatment.
Three people had an elongation of the QT_cF of QT_cI > 30 msec at various time points on atomoxetine 60 mg 2x daily compared to before the treatment.

Ethnicity: There were no significant differences between White and African patients.

Plasma concentrations:
The average of the maximum plasma concentration of atomoxetine was 827 ng/mL for 20 mg 2x daily and 2,770 ng/mL for 60 mg 2x daily. The maximum plasma concentrations were 1,711 ng/mL and 5,016 ng/mL respectively. The maximum values were achieved on average 2 hours after the dose.

Side effects:
There were no fatalities or medication-related severe adverse events. Three people terminated the study prematurely due to atomoxetine-related side effects (palpitations, dizziness and increased systolic blood pressure on atomoxetine 20 mg 2x daily and erectile dysfunction on atomoxetine 20 and 60 mg 2x daily). A total of 400 atomoxetine-related side effects occurred.

Failing positive control:
Moxifloxacin was included as a positive control, because torsade de pointes had been observed at therapeutic concentrations of moxifloxacin. However, the ΔQT_c for moxifloxacin 400 mg single dose also remained low (upper limit of the confidence interval < 10 msec). A greater effect was expected based on historical controls. ΔQT_c was significantly elongated for all time points and correction methods compared to placebo and a difference of 5 msec compared to placebo was detectable.

NOTE: Women are more susceptible to QT elongation than men.
</td>
<td></td>
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<tr>
<td>ref. 7
Matsui A et al. Pharmacokinetics, safety, and tolera-</td>
<td>4</td>
<td>49 healthy volunteers received atomoxetine 10, 20, 90 or 120 mg single dose (n=23) or 40 or 60 mg 2x daily for 7 days (n = 26). 5 volunteers did not complete the study. All volunteers were analysed for the safety data. Data were</td>
<td>Authors' conclusions: 'The CYP2D6*10/*10 subjects had 2.1- to 2.2-fold and 1.8-fold</td>
</tr>
</table>

<table>
<tr>
<td>bility of atomoxetine and effect of CYP2D6*10/*10 genotype in healthy Japanese men. J Clin Pharmacol 2012;52:388-403. PubMed PMID: 21543662.

ref. 7, continuation</td>
<td>IM: A

PM: A</td>
<td>compared to those from a study involving 27 patients in the United States, who received atomoxetine 10, 30, 60, 90 or 120 mg single dose (n=27) or atomoxetine 40 mg 2x daily or placebo for 7 days (n = 21). Relevant co-medication was excluded.
Kinetic data following administration of a single dose or repeated doses were comparable. Side effects occurred less frequently with repeated doses than with a single dose.

Genotyping:
<table>
<tr><td>Japanese, single dose
- 5x gene dose 2
- 6x gene dose 1.25
- 4x *10/*10
- 7x gene dose 1/0
- 1x gene dose 0.25</td><td>Japanese, repeated doses
- 6x gene dose 2
- 12x gene dose 1.25
- 5x *10/*10
- 3x gene dose 1/0</td><td>American

- 7x gene dose 2
- 9x gene dose 1/0
- 11x PM</td></tr>
</table>

Results:
<table>
<tr><td colspan="4">*10/*10 versus gene dose 2:</td></tr>
<tr><td></td><td>single dose</td><td></td><td>Value for gene dose 2</td></tr>
<tr><td rowspan="2">AUC</td><td>10 mg</td><td>x 2.2 (S)</td><td>0.331 µg.hour/mL</td></tr>
<tr><td>120 mg</td><td>x 2.1 (S)</td><td>4.69 µg.hour/mL</td></tr>
<tr><td colspan="4">Side effects:
For the single dose and multiple doses combined, there was no difference between *10/*10 and non-*10/*10 in frequency, severity and nature of the side effects (NS).</td></tr>
<tr><td colspan="4">For the AUC, the results were comparable following correction for dose and body weight.</td></tr>
</table>

<table>
<tr><td colspan="2">Clearance compared to *10/*10:</td></tr>
<tr><td>PM</td><td>reduced by more than a factor 4.1 (S)</td></tr>
</table>

NOTE: Genotyping was performed for *2 to *8, *10 and gene duplication.</td>
<td>higher area under the plasma concentration–time curve values relative to the CYP2D6*1/*1 and *1/*2 subjects and the CYP2D6*1/*10 and *2/*10 subjects, respectively. The adverse events reported by CYP2D6 *10/*10 subjects were indistinguishable from those of other Japanese participants. The higher mean exposure in CYP2D6*10/*10 subjects is not expected to be clinically significant.'

AUC atomoxetine versus gene dose 2:
IM: 215%</td>
</tr>
<tr>
<td>ref. 8
ter Laak MA et al. Recognition of impaired atomoxetine metabolism because of low CYP2D6 activity. Pediatr Neurol 2010;43:159-62. PubMed PMID: 20691935.</td>
<td>1

IM: AA</td>
<td>10 of the 100 children treated with standard doses of atomoxetine were genotyped due to side effects (gastrointestinal problems, sleep disorders, malaise, inactivity or mood instability) and/or a late response (> 9 weeks). 6 were CYP2D6 IM, the other 4 were CYP2D6 NM. The figure of 60% found for IM is numerically higher than the figure of 10% found in the Dutch population (significance not determined, NS).
For 2 IM and 1 NM with gene dose 1.25 or 1.5, the maintenance dose was increased prior to genotyping due to a delayed response. For 1 IM, the maintenance dose was reduced prior to genotyping without the side effects disappearing.
4 IM refused a lower dose and stopped the treatment due to side effects that initially occurred. For one IM, the dose was reduced back to the original maintenance dose of 40 mg/day (1.14 mg/kg per day). For another IM, the maintenance dose was reduced further to 25 mg/day (0.42 mg/kg per day). In both cases, this resulted in a good response and the new dose was tolerated well.
For the NM who was also CYP2C19 NM, the maintenance dose was increased to 60 mg/day (1.5 mg/kg per day). This resulted in a good response and good toleration of the treatment.</td>
<td>Authors' conclusions: 'We conclude that children on atomoxetine benefit from educating neurologists about the importance of cytochrome P450 polymorphisms, clinically recognizing patients with compromised atomoxetine metabolism, and (ideally) pretreatment genotyping of CYP2D6.'</td>
</tr>
</table>

ref. 8, continuation		The other 3 NM were CYP2C19 IM. For the two patients with CYP2D6 gene dose 1.25 or 1.5, a reduction in the maintenance dose (to 1.14 and 0.83 mg/kg per day) resulted in a good response and good toleration of the treatment. For the patient with CYP2D6 gene dose 2, switching from taking the atomoxetine in the morning to taking it in the evening was sufficient (dose 1.14 mg/kg per day). NOTE: Alleles *2 to *6, *9, *10 and *41 were genotyped.	
ref. 9 Ramoz N et al. A Haplotype of the Norepinephrine Transporter (Net) Gene Slc6a2 is Associated with Clinical Response to Atomoxetine in Attention-Deficit Hyperactivity Disorder (ADHD). Neuropsychopharmacology 2009;34:2135-42.	3 PM: AA	265 children with ADHD, 19x PM, 246x NM[#] (genotyped for *3-*8), who were treated with atomoxetine for 6 weeks (0.5-1.8 mg/kg per day), co-medication unknown. PM versus NM[#]: - no difference in efficacy of treatment (measured based on the severity of the ADHD symptoms after 6 weeks) (NS).	Authors' conclusions: 'Interindividual response was independent of the genetic variants of CYP2D6. The lack of effect of CYP2D6 metabolism status seen in this study may be due to small sample size as this has been previously shown in a larger population including some patients from this genetic cohort (Michelson et al, 2007).'
ref. 10 Trzepacz PT et al. CYP2D6 metabolizer status and atomoxetine dosing in children and adolescents with ADHD. Eur Neuropsychopharmacol 2008;18:79-86.	3 PM: A	1,326 children with ADHD, 87x PM, 1,239x NM[#] (genotyped for *3-*8), who were treated with atomoxetine for 10 weeks (dose titration based on effect and side effects without knowledge of the genotype; initial dose 0.5 mg/kg per day; maximum 1.8 mg/kg per day; weekly visits to a physician), only co-medication for psychiatric conditions was excluded. PM versus NM[#]: - Reduction in the average modal dose and the average final dose by 10% (S, from 1.26 to 1.14 mg/kg per day and from 1.5 to 1.35 mg/kg per day respectively). - No increase in the percentage responders (≥ 25% reduction in symptoms) (NS, from 81.6% to 84.9% respectively). No greater reduction in ADHD symptoms (NS, from 52% to 59%). There was a greater reduction in symptoms in the subcategory "lack of attention" (S, from 49% to 57%). - No increase in the incidence of side effects requiring treatment (including reduced appetite) (NS, from 57.5% to 54%). No increase in the percentage of patients who stopped taking part in the study due to side effects (NS, from 2.4% to 5.8%). No difference in the increase in height, DBP and SBP and QT_c interval. Increased weight loss by 366% (S, from weight gain of 1.0% to weight loss of 2.5%). Reduction in the percentage increase of the heart rate by 58% (S, from 8.5% to 13.4%). - Increase in the AUC calculated using a pharmacokinetic model in weeks 8-10 by 729% (from approx. 3 to approx. 25 µg.h/mL).	Authors' conclusions: 'Results suggest genotyping is unnecessary during routine clinical management, because investigators were able to dose atomoxetine to comparable efficacy and safety levels in NMs and PMs without knowledge of genotype metabolizer status.'
ref. 11 Cui YM et al. Atomoxetine pharmacokinetics in healthy Chinese	4	16 healthy volunteers, 7x IM (*10/*10), 9x NM (*1/*1 or *1/*10) (genotyped for *2-*11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29, *30, *31, *35, *36, *40 and *4), atomoxetine 40 mg/day for 3 days, followed by 80 mg/day for 7 days, no relevant co-medication;	Authors' conclusion: 'Whilst the number of homozygous CYP2D6*10 subjects was too small to

subjects and effect of the CYP2D6*10 allele. Br J Clin Pharmacol 2007;64:445-9. **ref. 11, continuation**	IM: A	IM versus NM: - Increase in AUC_{0-24h} by 119% (S, from 4,427 to 9,693 h/ng per mL). - Decrease in Cl_{or} by 55% (S, from 0.29 to 0.13 L/h per kg). - Increase in $t_{1/2}$ by 38% (S, from 3.74 to 5.17 h). - The same differences in AUC, Cl_{or} and $t_{1/2}$ after the first dose (S, change by 121%, 55% and 62% respectively). - No difference in frequency, severity and nature of the side effects. All side effects were mild and occurred only during the initial period. The most common side effects were dizziness, nausea and abdominal pain.	support definitive conclusions, higher average drug exposures in this group did not appear to result in differences in safety or tolerability.' AUC atomoxetine compared to NM: IM: 219%
ref. 12 Michelson D et al. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry 2007;46:242-51.	3 PM: AA[#] PM: B	589 children with ADHD, 30x PM, 559x NM[#] (genotyped for *3-*8), who were treated in 4 registration studies with atomoxetine for 6-8 weeks (dose titration based on effect and side effects without knowledge of the genotype; maximum 1.8 mg/kg per day), only co-medication for psychiatric conditions was excluded. Efficacy was also determined in two open label studies. Data about safety and side effects were determined for 3,524 children, 237x PM, 3017x NM[#]. In one safety study in which fluoxetine 20 mg/day was given as co-medication (n=141), 46 NM with atomoxetine plasma concentrations 2 SD lower than the average for a genotypically PM were included in the PM group. Analysis of the data without these 46 patients did not change the results. PM versus NM[#]: - Decrease in the final dose by 7% (NS, from 1.37 to 1.28 mg/kg per day). Open label studies: decrease in the final dose by 11% (S, from 1.5 to 1.33 mg/kg per day). Safety group: decrease in the final dose by 10% (NS, from 1.44 to 1.29 mg/kg per day). - Increase in the percentage responders (≥ 25% reduction in symptoms) by 35% (S, from 59.4% to 80% (placebo: 32.1%)). Open label studies: NS. Greater reduction in ADHD symptoms (S, from 35% to 54%). Open label studies: S, from 52% to 59%. Decrease in the percentage of patients who terminated treatment due to lack of efficacy by 33% (S; from 26.0% to 17.3%). - Increase in the incidence of tremor by 364% and of decreased appetite by 42% (S; from 1.1% to 5.1% and from 17% to 24.1% respectively). Increase in the incidence of abrasions by 132% and of insomnia by 54% (S; from 2.2% to 5.1% and from 6.8% to 10.5% respectively). The incidence of abrasions is probably not therapy-related. No increase in the percentage of patients who stopped taking part in the study due to side effects (NS, from 5.8% to 8.9%). No difference in the increase in height, SBP and QT_c interval. Decrease in weight gain by 34% (S, from 6.4% to 4.2%). Reduction in the percentage increase of the heart rate by 67% (S, from 7.1% to 11.9%). The differences in heart rate could be clinically relevant for patients with cardiac conditions. Reduction in the percentage increase of DBP by 64% (S, from 4.0% to 6.6%). - Increase in the peak concentrations at a dose of approx. 0.9 mg/kg per day by 409% (NS, from 167.1 to 850.6 ng/mL).	Authors' conclusion: 'These results suggest that CYP2D6 poor metabolizers taking atomoxetine in doses up to 1.8 mg/kg/day are likely to have greater efficacy, greater increases in cardiovascular tone, and some differences in tolerability compared with CYP2D6 normal metabolizers taking similar doses.'

ref. 13 Sauer JM et al. Disposition and metabolic fate of atomoxetine hydrochloride: the role of CYP2D6 in human disposition and metabolism. Drug Metab Dispos 2003;31:98-107.	3 PM: A	7 healthy volunteers, 3x PM, 4x NM# (genotyped for *3-*8, with distinction only between PM and the rest, phenotyped using dextromethorphan), 20 mg 2x daily atomoxetine for 6 days, co-medication unknown (significance unknown for all); - PM: increase in AUC for atomoxetine versus NM# from 1.08 to 8.44 µg·h/mL (S by 681%), increase in $C_{ss,max}$ from 160 to 915 ng/mL (by 473%), increase in t½ from 5.34 to 20.0 hours, decrease in Cl_{or} from 0.737 to 0.0357 L/h/kg (by 95%). 4-HA below detection limit. Increase in AUC for N-DA versus NM# from 0.0618 to 2.82 µg·h/mL (by 4,463%), increase in $C_{ss,max}$ from 7.02 to 259.22 ng/mL (by 3,593%), increase in t½ from 8.97 to 33.3 hours.	AUC atomoxetine + 4-HA compared to NM#: PM: 781%
ref. 14 SmPC Strattera (atomoxetine-hydrochloride) 01-01-16.	0 PM: B	<u>Dose</u>: Approximately 7% of the White population has a genotype that corresponds to a non-functional CYP2D6 enzyme (called CYP2D6 poor metabolisers). Patents with this genotype experience a much higher exposure to atomoxetine than patients who have a functional enzyme. Therefore, poor metabolisers have an increased risk of side effects. A lower initial dose and slower dose titration should be considered for patients who are known to have poor metabolism. <u>Side effects</u>: *Paediatric patients* The following side effects occurred in at least 2% of all patients who metabolise CYP2D6 slowly (poor metabolisers, PMs) and were statistically significantly more frequent in PMs than in patients who metabolise CYP2D6 fast (normal metabolisers, NMs): decreased appetite (24.1% of PMs, 17.0% of NMs); insomnia combined (includes insomnia, problems sleeping through the night and being unable to fall asleep, 14.9% of PMs, 9.7% of NMs); depression combined (includes depression, major depression, depressive symptoms, depressive mood and dysphoria, 6.5% of PMs and 4.1% of NMs); weight loss (7.3% of PMs, 4.4% of NMs); constipation (6.8% of PMs, 4.3% of NMs); tremor (4.5% of PMs, 0.9% of NMs); sedation (3.9% of PMs, 2.1% of NMs); abrasions (3.9% of PMs, 1.7% of NMs); enuresis (3.0% of PMs, 1.2% of NMs); conjunctivitis (2.5% of PMs, 1.2% of NMs); syncope (2.5% of PMs, 0.7% of NMs); early waking in the morning (2.3% of PMs, 0.8% of NMs); mydriasis (2.0% of PMs, 0.6% of NMs). The following side effect did not meet the abovementioned criteria, but was noteworthy: generalised anxiety disorder (0.8% of PMs and 0.1% of NMs). In addition, weight loss was more pronounced in PM patients in studies that lasted up to 10 weeks (mean 0.6 kg for NMs and 1.1 kg for PMs). *Adults* The following side effects occurred in at least 2% of all patients who metabolise CYP2D6 slowly (poor metabolisers, PMs) and were statistically significantly more frequent in PMs than in patients who metabolise CYP2D6 fast (normal metabolisers, NMs): blurred vision (3.9% of PMs, 1.3% of NMs), dry mouth (34.5% of PMs, 17.4% of NMs), constipation (11.3% of PMs, 6.7% of NMs), feeling jittery (4.9% of PMs, 1.9% of NMs), decreased appetite (23.2% of PMs, 14.7% of NMs), tremor (5.4% of PMs, 1.2% of NMs), insomnia (19.2% of PMs, 11.3% of NMs), sleep disorder (6.9% of PMs, 3.4% of NMs), problems sleeping through the night (5.4% of PMs, 2.7% of NMs), early waking in the morning (3% of PMs, 0.9% of NMs), urine retention (5.9% of PMs, 1.2% of NMs), erectile dysfunction (20.9% of PMs, 8.9% of NMs), ejaculation disorder (6.1% of PMs, 2.2% of	

ref. 14, continuation		NMs), hyperhidrosis (14.8% of PMs, 6.8% of NMs), peripheral coldness (3% of PMs, 0.5% of NMs). Pharmacodynamic properties A thorough QT/QTc study, performed on healthy adults who metabolised CYP2D6 poorly, with doses up to 60 mg atomoxetine twice daily, demonstrated that the effect of atomoxetine on the QTc interval at maximum expected concentrations did not differ significantly from placebo. There was a slight elongation of the QTc interval with elevated atomoxetine concentration. Pharmacokinetic data Atomoxetine undergoes biotransformation primarily by cytochrome P450 2D6 (CYP2D6) enzymes. Individuals with a reduced activity of these enzymes (poor metabolisers) represent approximately 7% of the White population and have a higher plasma concentration of atomoxetine compared to individuals who have normal activity (normal metabolisers). For poor metabolisers, the AUC of atomoxetine is approximately 10 times greater and the Css, max is approximately 5 times higher than for normal metabolisers. The most important oxidative metabolite that is formed is 4-hydroxyatomoxetine, which rapidly undergoes glucuronidation. 4-Hydroxyatomoxetine is equipotent to atomoxetine, but circulates in much lower concentrations in the plasma. Although 4-hydroxyatomoxetine is primarily formed by CYP2D6, in individuals who lack CYP2D6 activity it can be formed by various other cytochrome P450 enzymes, but at a much slower rate.	AUC atomoxetine compared to NM: PM: about 1000%
ref. 15 SmPC Strattera (atomoxetine) 25-02-20, USA.	1 PM: B	Dose: In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients who are known to be CYP2D6 PMs, Strattera should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, Strattera should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. Warnings: Routine laboratory tests are not required. Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of Strattera compared with normal metabolisers (NMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of Strattera. Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. Dosage adjustment of Strattera may be necessary when coadministered with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, and quinidine) or when administered to CYP2D6. Adverse reactions: The following adverse reactions occurred in at least 2% of child and adolescent CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 NM patients: insomnia (11% of PMs, 6% of NMs); weight decreased (7% of PMs, 4% of NMs); consti-	

ref. 15, continuation		pation (7% of PMs, 4% of NMs); depression (includes the following terms: depression, major depression, depressive symptoms, depressed mood, dysphoria) (7% of PMs, 4% of NMs); tremor (5% of PMs, 1% of NMs); excoriation (4% of PMs, 2% of NMs); middle insomnia (3% of PMs, 1% of NMs); conjunctivitis (3% of PMs, 1% of NMs); syncope (3% of PMs, 1% of NMs); early morning awaking (2% of PMs, 1% of NMs); mydriasis (2% of PMs, 1% of NMs); sedation (4% of PMs, 2% of NMs). The following adverse events occurred in at least 2% of adult CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared to CYP2D6 normal metaboliser (NM) patients: vision blurred (4% of PMs, 1% of NMs); dry mouth (35% of PMs, 17% of NMs); constipation (11% of PMs, 7% of NMs); feeling jittery (5% of PMs, 2% of NMs); decreased appetite (23% of PMs, 15% of NMs); tremor (5% of PMs, 1% of NMs); insomnia (19% of PMs, 11% of NMs); sleep disorder (7% of PMs, 3% of NMs); middle insomnia (5% of PMs, 3% of NMs); terminal insomnia (3% of PMs, 1% of NMs); urinary retention (6% of PMs, 1% of NMs); erectile dysfunction (21% of PMs, 9% of NMs); ejaculation disorder (6% of PMs, 2% of NMs); hyperhidrosis (15% of PMs, 7% of NMs); peripheral coldness (3% of PMs, 1% of NMs). <u>Pharmacodynamics</u>: The effect of Strattera on QTc elongation was evaluated in a randomized, double-blinded, positive- (moxifloxacin 400 mg) and placebo-controlled, cross-over study in healthy male CYP2D6 poor metabolisers. A total of 120 healthy subjects were administered Strattera (20 mg and 60 mg) twice daily for 7 days. No large changes in QTc interval (i.e., increases > 60 msec from baseline, absolute QTc > 480 msec) were observed in the study. However, small changes in QTc interval cannot be excluded from the current study, because the study failed to demonstrate assay sensitivity. There was a slight increase in QTc interval with increased atomoxetine concentration. <u>Pharmacokinetics</u>: Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (NMs). For PMs, AUC of atomoxetine is approximately 10-fold and Css, max is about 5-fold greater than NMs. Laboratory tests are available to identify CYP2D6 PMs. The major oxidative metabolite formed, regardless of CYP-2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in NMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in NMs and 45% of atomoxetine concentration in PMs).	AUC atomoxetine compared to NM: PM: about 1000%
ref. 16 Data on file, Lilly Research Laboratories, 2006.	0	<u>Dose titration:</u> 1,216 patients, 85x PM and 1,131x NM, titration based on clinical response; - Dose reduction for PM compared to NM from 1.30 to	conclusion Eli Lilly: 'A review of clinical trial data strongly supports the safety of

Atomoxetine – comparison of data of normal metaboliser and poor metaboliser patients. **ref. 16, continuation**	PM: B	1.24 mg/kg/day, difference is NS. <u>Safety analysis:</u> 3,138 patients, 228x PM and 2,910x NM, sub-group > 6 months of treatment is 90x PM and 1,245x NM; Reported side effects in ≥ 2% of NM and/or PM: - decreased appetite, insomnia, sedation, depression, tremor, early waking in the morning, mydriasis and pruritis are significantly more common in PM than in NM. - In the sub-group > 6 months, "chest discomfort", laryngitis and vasovagal collapse were significantly more common in PM than in NM. Repolarisation, 100 patients: - no significant relationship between C_{ss} atomoxetine and the QT_c time. Vital signs and weight: - Increase in heart rate versus NM from 6.7 to 10.3 bpm (S), increase in SBP from 2.6 to 3.8 mmHg (NS), DBP from 4.3 to 2.7 mmHg (S). Weight loss of 0.2 kg for PM versus weight gain of 1.1 kg for NM (S). - In sub-group > 6 months: increase in heart rate versus NM from 6.8 to 11.1 bpm (S) and reduction in weight gain from 3.0 to 0.7 kg (S). Termination of treatment versus NM: - Increase in termination of treatment due to side effects from 5 to 7.5% (NS). Constipation is listed as the cause significantly more often for PMs. - In the sub-group > 6 months there was a reduction in termination due to side effects: from 1.6 to 0% (NS) - Reduction in termination due to lack of effect from 7.3 to 3.3%. <u>Efficacy</u> Placebo-controlled studies, 15x PM, 277x NM and 143x placebo; - ADHD-RS score decreased more markedly for PM than for NM (-24.1 versus -14.4, S). Meta-analysis of open-label trials, 86x PM and 1,232x NM; - ADHD-RS score decreased more markedly for PM than for NM (-22.2 versus -19.9, S).	usual doses of atomoxetine in poor metaboliser (PM) patients. In fact, at usual doses there appears to be an increased benefit in PM patients as compared to normal metaboliser patients.'

NM[#]: All phenotypes other than PM. NM[#] is therefore equal to IM, NM and UM. Phenotyping can only distinguish between PM and the other phenotypes.

AA[#]: There is a significant difference between NM and PM, but the clinical effect is more favourable for PM than for NM. As the purpose of classification of the severity of the effect is to classify negative effects, code AA is used for a positive effect.

Risk group	IMs with CYP2D6 inhibitor

Comments:

- Barrie 2018 (Barrie ES et al. Testing genetic modifiers of behavior and response to atomoxetine in autism spectrum disorder with ADHD. J Dev Phys Disabil 2018;30:355-71. PMID: 30197492) was not included in the risk analysis, because there are too many uncertainties in the article for the data to be reliable. The genotype-phenotype definition is not clear from the article. The authors refer to the CPIC-guideline for CYP2D6 and codeine, which defined genotypes with gene dose 1 as normal metabolisers before 2019. However, the IM/NM-ratio of 0.68 reported by the authors is much higher than expected when using this definition, which includes the majority of IM (gene dose 1) in the NM-group. In addition, the authors refer to *2 as an allele with reduced function, which it is not, also not according to the CPIC-guideline. Furthermore, the authors report 11.5% of patients to be UM, but do not report gene duplication to be determined, and claim to have determined a single nucleotide polymorphism that enhances CYP2D6 enzyme activity (rs5758550, which according to Dinh JC et al. Clin Pharmacol Ther 2021 Oct 30 [Epub ahead of print] has little or no effect on in vitro atomoxetine metabolism). Finally, the authors claim to report only data in White patients. However, for atomoxetine, they state that 48 users were White, but report data for 52 users.

- The data from the American SmPC are also described by Allen et al. (Biol Psychiatry 2002;51 [suppl8]: 37S) and in a review by Wernicke et al. (J Clin Psychiatry 2002;63 Suppl 12:50-5): 67 PMs were compared to 1,290 NMs who were using atomoxetine ≥ 1.2 mg/kg/day: no difference versus NM in average dose of atomoxetine, QTc interval, blood pressure, termination of the treatment due to side effects or the occurrence of side effects (except headache). Significant increase versus NM in the reduction of ADHD symptoms, weight (from +0.6 to -0.7), increase in heart rate (from 6.2 to 10.3 bpm) and the occurrence of headache.
- Existing guidelines:

  Brown JT et al. Clinical Pharmacogenetics Implementation Consortium guideline for cytochrome P450 (CYP)-2D6 genotype and atomoxetine therapy. Clin Pharmacol Ther 2019;106:94-102. PMID: 30801677 and change in CYP2D6 genotype to phenotype translation on the CPIC website in October 2019 (https://cpicpgx.org/guidelines/cpic-guideline-for-atomoxetine-based-on-cyp2d6-genotype/).

  CPIC indicates that although not routinely ordered, patients may benefit from a single time point atomoxetine exposure check to guide therapy. Exposure check concentrations between 200-1000 ng/mL are generally considered to be “therapeutic” (Michelson 2007 and Hiemke C et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018;51:el). however for individuals with comorbidities a higher exposure target may be warranted, as was done in a study evaluating children with both ADHD and Oppositional Defiant Disorder (Hazell P et al. Relationship between atomoxetine plasma concentration, treatment response and tolerability in attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. Atten Defic Hyperact Disord 2009;1:201–10). CPIC proposes that the plasma concentration exposure check be used with an individual’s CYP2D6 genotype to help clinicians guide dose selection and titration. Based on pharmacokinetic knowledge that CYP2D6 metabolism phenotypes influence atomoxetine peak concentration and half-life, CPIC proposes that prescribers consider measuring peak concentrations 1 to 2 hours after dosing in known CYP2D6 UMs, NMs and IMs with high activity (activity score 1.0), 2 to 4 hours after dosing in CYP2D6 IMs with low activity (activity score 0.25-0.75), and 4 hours after dosing in PMs.

  For UM + gene dose 2.5, CPIC indicates that very limited data exist, but that it is unlikely that these individuals would achieve adequate serum concentrations with standard atomoxetine dosing (de Leon J. Translating pharmacogenetics to clinical practice: do cytochrome P450 2D6 ultrarapid metabolizers need higher atomoxetine doses? J Am Acad Child Adolesc Psychiatry 2015;54:532-4). CYP2D6 non-PMs have a lower likelihood of treatment response as compared to CYP2D6 PMs (Michelson 2007). Thus, for CYP2D6 UMs, CPIC recommends to initiate standard atomoxetine dosing, and if no clinical response is observed after two weeks, to consider obtaining a peak plasma concentration one to two hours after dose administration. If the peak concentration is less than 200 ng/ml, CPIC recommends considering increasing the dose proportionally to approach 400 ng/ml (Michelson 2007). CPIC indicates that it is important to note that doses above 120 mg have not been extensively evaluated, although they may be necessary to achieve target concentrations in some patients. CPIC considers the strength of the recommendation for UM + gene dose 2.5 to be moderate, indicating that “there is a close or uncertain balance” as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

  For NM, CPIC give the same recommendation as for UM + gene dose 2.5, based on the observed lower likelihood of treatment response for CYP2D6 non-PMs compared to CYP2D6 PMs (Michelson 2007). CPIC considers the strength of this recommendation to be moderate, indicating that “there is a close or uncertain balance” as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

  For PM, CPIC indicates that atomoxetine exposure (AUC) is, on average, 10-fold higher in CYP2D6 PMs compared to non-PMs (Brown 2016, Trzepacz 2008, Michelson 2007, Sauer 2003, and Ring BJ et al. Identification of the human cytochromes P450 responsible for atomoxetine metabolism. Drug Metab Dispos 2002;30:319-23). In addition, CPIC indicates that the likelihood of favourable treatment response and side effects are both reported to be higher in CYP2D6 PMs compared to non-PMs, which is likely due to increased exposure to parent drug in the PMs. The extent of improvement in ADHD symptoms, i.e. mean change in ADHD symptom rating scale scores, was greater in PMs compared to non-PMs, while CYP2D6 non-PMs were also more likely to discontinue atomoxetine therapy due to inefficacy as compared to CYP2D6 PMs (Michelson 2007). Higher exposures to atomoxetine may also partially explain a greater percentage of side effects in CYP2D6 PMs, such as increases in heart rate and diastolic blood pressure, when compared to non-PMs (Fijal 2015, Trzepacz 2008, and Michelson 2007). Therefore, the CPIC recommendation for PM is to initiate with a standard starting dose and if there is an inadequate trajectory of symptom improvement after 2 weeks (in the absence of side effects), to consider obtaining a plasma concentration two-four hours after dosing. If response is inadequate and side effects are not present, CPIC recommends to consider adjusting the dose proportionally to approach 400 ng/ml. For children, CPIC considers the strength of the recommendation to be strong, indicating that the evidence is high quality and the desirable effects clearly outweigh the undesirable effects. For adults, CPIC considers the strength of the recommendation to be moderate, indicating that “there is a close or uncertain balance” as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

  For IM, CPIC indicates that ex vivo studies evaluating metabolic capacity in human liver microsomes that have been genotyped for CYP2D6 provide evidence that increased exposure is due to reduced metabolic capacity in both IMs and PMs (Dinh JC et al. Characterization of atomoxetine biotransformation and implications for development of PBPK models for dose individualization in children. Drug Metab Dispos 2016;44:1070–9; Monroe

WM. Fifty years of change. Va Med 1989;116:281–2; and Farid NA et al. Single-dose and steady-state pharmacokinetics of tomoxetine in normal subjects. J Clin Pharmacol 1985;25:296–301). In addition, CPIC indicates that individuals with two CYP2D6*10 alleles (gene dose 0.5) had higher atomoxetine exposure (5-fold higher peak concentration) when compared to individuals with at least one normal function allele (Byeon 2015, Matsui 2012, and Cui 2007). Concerning clinical effects, CPIC indicates that current evidence is limited to comparisons between CYP2D6 PMs and non-PMs; thus, there is no evidence correlating efficacy and/or drug discontinuation with other CYP2D6 phenotype classes. CPIC indicates that while IMs with activity scores of 1 have higher atomoxetine plasma concentrations compared to NMs with an activity score of 2, the clinical significance of this difference is unclear. Thus, CPIC concludes that IMs with an activity of 1 should be treated similarly to NMs. CPIC considers the strength of this recommendation to be moderate, indicating that "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

For IMs with gene dose 0.25-0.75, CPIC indicates that, like PMs, they have significantly decreased metabolism of atomoxetine, which may increase the risk of side effects (Fijal 2015, Trzepacz 2008, and Michelson 2007). However, these individuals may also have greater improvement of ADHD symptoms and lower dose requirements as compared to non-PMs. Therefore, CPIC decided to give the same recommendation for IM with gene dose 0.25-0.75 as for PM. CPIC considers the strength of this recommendation for IMs with gene dose 0.25-0.75 to be moderate, indicating that "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

The recommendations are as follows:

phenotype	activity score of subgroup	children[a]		adults[a]	
		therapeutic recommendation	classification of recommendation	therapeutic recommendation	classification of recommendation
UM+ gene dose 2.5		Initiate with a dose of 0.5 mg/kg/day and increase to 1.2 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml.[b,c]	moderate	Initiate with a dose of 40 mg/day and increase to 80 mg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider increasing dose to 100 mg/day. If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml.[b,c] Dosages greater than 100 mg/day may be needed to achieve target concentrations.[d]	moderate
NM		Initiate with a dose of 0.5 mg/kg and increase to 1.2 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml.[b,c]	moderate	Initiate with a dose of 40 mg/day and increase to 80 mg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider increasing dose to 100 mg/day. If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml.[b,c] Dosages greater than 100 mg/day may be needed to	moderate

				achieve target concentrations.[d]	
IM	1	Initiate with a dose of 0.5 mg/kg and increase to 1.2 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml.[b,c]	moderate	Initiate with a dose of 40 mg/day and increase to 80 mg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider increasing dose to 100 mg/day. If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml.[b,c] Dosages greater than 100 mg/day may be needed to achieve target concentrations.[d]	moderate
	0.25-0.75	Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 2–4 h after dosing. If response is inadequate and concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml.[b,c] If unacceptable side effects are present at any time, consider a reduction in dose.	moderate	Initiate with a dose of 40 mg/day and if no clinical response and in the absence of adverse events after 2 weeks increase dose to 80 mg/day. If response is inadequate after 2 weeks consider obtaining a plasma concentration 2–4 h after dosing. If concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml.[b,c] If unacceptable side effects are present at any time, consider a reduction in dose.	moderate
PM		Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 4 h after dosing. If response is inadequate and concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml.[b,c] If unacceptable side effects are present at any time, consider a reduction in dose.	strong	Initiate with a dose of 40 mg/day and if no clinical response and in the absence of adverse events after 2 weeks increase dose to 80 mg/day. If response is inadequate after 2 weeks consider obtaining a plasma concentration 2–4 h after dosing. If concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml.[b,c] If unacceptable side effects are present at any time, consider a reduction in dose.	moderate

[a] The recommended initial dose is 0.5 mg/kg/day for children and 40 mg/day for adults, and the recommended target and maximum dose are 1.2 mg/kg/day and 1.4 mg/kg/day in children, and 80 mg/day and 100 mg/day in adults.

[b] Therapeutic range of 200 to 1000 ng/ml has been proposed (Schoretsanitis G et al. TDM in psychiatry and neurology: A comprehensive summary of the consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology, update 2017; a tool for clinicians. World J Biol Psychiatry 2018;19:162-74).

[c] Limited data are available regarding the relationship between atomoxetine plasma concentrations and clinical response. Available information suggests that clinical response is greater in PMs compared to non-PMs and may be related to the higher plasma concentrations 1 to 1.5 hours after dosing in PMs compared to non-PMs administered a similar dose.

Furthermore, modest improvement in response, defined as reduction in ADHD-RS, is observed at peak concentrations greater than 400 ng/ml.

[d] Doses above 120 mg/day have not been evaluated.

The CPIC guideline is based on 10 of the 13 articles included in our risk analysis. Jung 2020 and Kim 2018 are not included in the CPIC guideline yet, because the search for this guideline was done in August 2018. In addition, Loghin 2013 was not included in the CPIC guideline. The following studies are included in the CPIC guideline and not in our risk analysis: 2 *in vitro* studies, 4 additional *ex vivo*/clinical studies, 6 studies investigating the effect of CYP2D6 inhibitors instead of CYP2D6 genotype, and 1 additional clinical study (Asherson P et al. Efficacy of atomoxetine in adults with attention deficit hyperactivity disorder: an integrated analysis of the complete database of multicenter placebo-controlled trials. J Psychopharmacol 2014;28:837-46 (CYP2D6 not mentioned in abstract, showed no clinically relevant differences in the efficacy of atomoxetine between subgroups based on CYP2D6 status)).

On 7-12-2021, there was not a more recent version of the recommendations present on the CPIC-site.

Date of literature search: 20 November 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4 B	yes	yes	31 January 2022
	IM	4 B	yes	yes	
	UM	3 AA	yes	yes	

Mechanism:

Atomoxetine is primarily metabolised by CYP2D6 to 4-hydroxyatomoxetine. This metabolite is equipotent to atomoxetine, but circulates in much lower concentrations in the plasma.

The enzyme CYP2C19 and other iso-enzymes form N-desmethylatomoxetine, which is virtually inactive. In NMs, 5% of the atomoxetine is converted to N-desmethylatomoxetine, in PMs this figure is 45%.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	Possible Score	Given Score
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	+
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	

Total Score:	10+	1+
Corresponding Clinical Implication Score:		Potentially beneficial