CYP3A4: quetiapine 5991/5992

IM = intermediate metaboliser (*1/*22; reduced CYP3A4 enzyme activity), NM = normal metaboliser (*1/*1, normal CYP3A4 enzyme activity), PM = poor metaboliser (*22/*22; strongly reduced CYP3A4 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:
A total of 90% of quetiapine is metabolised by CYP3A4. This results in the formation of the inactive metabolite quetiapine sulfoxide and the formation of the metabolite N-desalkylquetiapine (norquetiapine). N-desalkylquetiapine is active, but seems to have mainly anti-depressive activity.
The NVZA (Dutch association of hospital pharmacists) mentions the therapeutic range to be 50-500 µg/L in general, however with large interindividual variation, and states that toxic concentrations are not known. The NVZA states that there is insufficient evidence to recommend an optimal trough plasma concentration of quetiapine, due to the weak relation between plasma concentration and clinical effect. It seems that in general a plasma concentration of 50-500 ng/ml belongs to a therapeutic dose of 200-800 mg quetiapine per day. However, higher concentrations have been measured in patients without toxic effects. Reference values for the active metabolite N-desalkylquetiapine are still scarce. Routine therapeutic drug monitoring is not recommended for quetiapine.
In literature, a therapeutic range of quetiapine of 100-500 µg/L with toxic concentrations > 1000 µg/L, and a therapeutic range of 100-250 µg/L for N-desalkylquetiapine is mentioned (Hiemke C et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018; 51:9-62).
When treatment was set for 238 patients based on clinical effect, the percentage of patients with a plasma concentration of quetiapine above 500 µg/L was a factor 5.6 higher for IM+PM. The dose-corrected plasma concentration was a factor 3.2 higher for PM and a factor 1.2 higher for IM compared to NM. There have been no studies into the effect of the CYP3A4 genotype on side effects or effectiveness. Therefore, it is not known whether the gene-drug interaction has any clinical consequences. However, whereas IM phenotype had a mild impact on the exposure of quetiapine, the impact of the PM phenotype was large, also compared to the width of the proposed therapeutic ranges (a factor of 5-10 between the lower and upper limit for quetiapine and a factor of 2.5 for the active metabolite N-desalkylquetiapine).
For these reasons, the KNMP Pharmacogenetics Working Group concluded the presence of a CYP3A4-quetiapine interaction and decided to recommend therapy adjustment for PM (yes/yes-interaction), but no therapy adjustment for IM (yes/no-interaction).
For PM, the observed 3.2 fold exposure increase corresponds to a calculated reduction of the dose to 31% of the normal dose. This was translated to a reduction to 30% of the normal dose to be more feasible in clinical practice.
Because formation of N-desalkylquetiapine should be reduced in PM, anti-depressive activity should be diminished in this phenotype. For this reason, the KNMP Pharmacogenetics Working Group recommends an alternative for the treatment of depression in CYP3A4 PM.
An overview of the clinical and kinetic effects per genotype is provided in the summary of the article below, or in the background information text of the relevant pharmacogenetic guideline in the KNMP Kennisbank. You may also have access to this background text via your pharmacy or physician information system.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting quetiapine to be potentially beneficial for prevention of adverse events and for 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 0 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):
There were no studies investigating the effect of variant CYP3A4 phenotypes on clinical effects. As a result, the maximum severity code was A 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 evidence for 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) Seroquel (quetiapine) 06-06-21 does not mention a genotype-predicted CYP3A4 phenotype or CYP3A4 gene variant. This 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 SmPC (only points for at least one genotype/phenotype mentioned in the SmPC).

The table below uses the KNMP nomenclature for NM, PM and IM. As a result, the nomenclature of the genotype groups in the table below can differ from the nomenclature used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 van der Weide K et al. The influence of the CYP3A4*22 polymorphism on serum concentration of quetiapine in psychiatric patients. J Clin Psychopharmacol 2014;34:256-60. PubMed PMID: 24525658. And personal communication (mean dose-corrected plasma concentrations).	4 IM: A PM: A	Plasma concentrations of quetiapine were determined in 238 patients during the first blood sample collection for therapeutic drug monitoring. The dose varied from 12.5 - 1,200 mg/day. Co-medication with an effect on CYP3A4 was not excluded. However, an analysis with exclusion of patients with such medication yielded the same results. Genotyping: - 207x NM - 29x IM - 2x PM Results: Percentage of patients with a plasma concentration above the therapeutic range (> 500 µg/L) versus NM (2.9%) IM+PM: x 5.55 (S) The plasma concentration was above the therapeutic range for both PMs and 10.3% of the IMs. Median dose-corrected plasma concentration compared to NM (0.36 µg/L per mg) IM: x 1.47 PM: x 4.81 S for IM+PM versus NM: *22 explained 3% of the variation in the (dose-corrected) plasma concentration. The dose explained 30% of the variation in the plasma concentration. Mean dose-corrected plasma concentration compared to NM (0.54 µg/L per mg) IM: x 1.20 PM: x 3.20 NS (significance not determined) Median daily dose versus NM (300 mg/day) IM+PM: NS	Authors' conclusion: 'Being a carrier of the CYP3A4*22 allele increases the serum concentration of quetiapine at comparable doses. …. Although it is not evident that the difference in serum levels between carriers and wild-type patients is clinically relevant, the even larger increase in concentration in homozygous mutant patients may well be relevant, but should be investigated in a larger study.' Dose-corrected C_{ss} versus NM: IM: 120% PM: 320%

Risk group	IMs and PMs with CYP3A4 inhibitor

Comments:

- The study of Saiz-Rodríguez 2020 (Saiz-Rodríguez M et al. Effect of the most relevant CYP3A4 and CYP-3A5 polymorphisms on the pharmacokinetic parameters of 10 CYP3A substrates. Biomedicines 2020;8:94. PMID: 32331352) investigating pharmacokinetics in 19 healthy volunteers receiving a single dose of quetiapine was not included in the risk analysis, because the genotype of the two variant allele carriers was not reported. For this reason, it was not known whether both variant allele carriers were IM or whether one was PM. In addition, it was not known whether the variant alleles concerned *22 (the most important variant allele

in the Netherlands), *20 (more deficient than *22 and very rare outside of Spain, so less important for the Dutch situation), or *3.

Date of literature search: 3 August 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4 A	yes	yes	13 September 2021
	IM	4 A	yes	no	

Mechanism:
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Quetiapine has various indications, which differ in the required dose and the active substance.
Quetiapine itself is responsible for the anti-psychotic effect. However, it has a low affinity for D2 receptors, meaning that high doses are required, often higher than the registered maximum (750 mg/day for immediate release, 800 mg/day for controlled release).
The active metabolite N-desalkylquetiapine (norquetiapine) is probably responsible for the anti-depressant effect. In contrast to quetiapine, the metabolite is a strong noradrenaline re-uptake inhibitor and a partial agonist of the 5-hydroxytryptamine-1A-receptor (one of the serotonin receptors). The dose as anti-depressant is usually 200-300 mg/day (maximum of 600 mg/day).
Quetiapine is also used as a sedative at low doses. Quetiapine binds to the H1 receptor in this case. The effect probably disappears at higher doses.

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+	0+
Corresponding Clinical Implication Score:		Potentially beneficial