CYP2D6: brexpiprazole 7046/7047/7048

AUC = area under the concentration-time curve, EPAR = European Public Assessment Report, IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (increased CYP2D6 enzyme activity)

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

Brief summary and justification of choices:
Brexpiprazol is mainly converted by CYP2D6 and CYP3A4 to the inactive metabolite DM-3411.The presence of genetic variants of CYP2D6 can result in either an absent or reduced CYP2D6 enzyme activity (poor or intermediate metabolisers (PM or IM)) or an increased CYP2D6 enzyme activity (ultrarapid metaboliser (UM)).

PM: The SmPCs and EPAR of brexpiprazole report higher brexpiprazole exposure in PM and recommend to halve the dose in these patients. At the moment, there are no articles supporting this for PM, but Ishigooka 2018 suggests an increased exposure for IM and thus a gene-drug interaction. In addition, the SmPCs also report a doubling of exposure in patients co-medicated with the strong CYP2D6 inhibitor quinidine, which can change a normal metaboliser phenotype into a poor metaboliser phenotype. Despite the very limited evidence, the KNMP Pharmacogenetics Working Group decided that a gene-drug interaction is likely and that PM patients are likely to benefit from halving of the normal dose (yes/yes-interaction).
Note: According to the SmPCs, halving the dose in case of co-medication with strong CYP3A4 inhibitors is recommended for both PM and normal metabolisers (NM). Because there is no difference between PM and NM in this respect, strong CYP3A4 inhibitors are not included in the therapeutic recommendation for PM.

IM: Ishigooka 2018 suggests an increased exposure for IM, but due to the limited size of the study significance is not reached. In addition, there is no evidence for a clinical effect in the study. 3 IM on the maximum brexpiprazole dose and 2 IM on 1.5 times the maximum dose did not develop serious adverse events. The SmPCs also do not recommend a dose reduction for IM. For these reasons, the KNMP Pharmacogenetics Working Group decided that there is insufficient evidence for a therapeutic recommendation for IM (yes/no-interaction).

UM: The EPAR reports a decrease of brexpiprazole AUC with 21%, based on a population pharmacokinetic model. This decrease is relatively small and there is no evidence for a negative effect on efficacy. Correspondingly, the SmPCs do not recommend therapy adjustment for UM. For these reasons, the KNMP Pharmacogenetics Working Group decided that there is insufficient evidence for a need for therapy adjustment for UM (yes/no-interaction).

You can find an overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions in 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 brexpiprazole to be potentially beneficial for prevention of adverse events. 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) (see also the clinical implication score tables at the end of this risk analysis):
There are no reports of clinical effects in users of brexpiprazole with a variant phenotype. Thus, the maximum severity code was A, corresponding to CTCAE grade 0. 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 clinical effect code ≥ D (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 brexpiprazole indicates that the dose should be halved for patients known to be CYP2D6 PM, but does not mention PM as a contra-indication nor recommends to genotype before starting brexpiprazole. 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 in the corresponding section 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.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr>
<td>ref. 1
Ishigooka J et al. Pharmacokinetics and safety of brexpiprazole following multiple-dose administration to Japanese patients with schizophrenia.
J Clin Pharmacol 2018;58:74-80.
PubMed PMID: 28750151.</td>
<td>4

IM: AA</td>
<td>21 patients were treated with brexpiprazole for 14 days. 7 patients were treated with a dose of 1 mg/day, 8 with a dose of 4 mg/day, and 6 with a dose of 6 mg/day. The follow-up period after treatment was 30 days.
The trough plasma concentration reached steady state after day 10 in all dose groups and genotypes. The AUC of brexpiprazole showed dose-proportionality.
The effect of genotype on adverse events was not studied, but all doses of brexpiprazole were well tolerated with no serious treatment-emergent adverse events occurring, except for worsening of schizophrenia in two patients resulting in treatment discontinuation. The most common treatment-emergent adverse event was an increase in serum prolactin level.
Relevant co-medication was excluded.

Genotyping:
<table>
<tr><td>1 mg/day</td><td>4 mg/day</td><td>6 mg/day</td></tr>
<tr><td>- 6x NM+IM</td><td>- 5x NM+IM</td><td>- 4x NM+IM</td></tr>
<tr><td>- 1x IM</td><td>- 3x IM</td><td>- 2x IM</td></tr>
</table>
Note: NM+IM = NM (gene dose 1.25-2) + gene dose 1/0
IM = gene dose 0.25-0.75 + gene dose 0.5/0.5
Two patients from the NM+IM group (1 on 1 mg/day and 1 on 4 mg/day) discontinued before day 14 due to worsening of schizophrenia.

Results:
<table>
<tr><td colspan="4">IM compared to NM+IM:</td></tr>
<tr><td></td><td></td><td>IM</td><td>value for NM+IM</td></tr>
<tr><td rowspan="2">dose-corrected AUC_{0-24h} (in ng.h/ml.mg)</td><td>day 1</td><td>x 1.47 (NS)</td><td>146</td></tr>
<tr><td>day 14</td><td>x 2.39 (NS)</td><td>462</td></tr>
</table>
Note: Genotyping was for *2, *4, *5, *10, *14A, *14B, *18, *21, and *41. These are the most important gene variants in this Japanese population.</td>
<td>Authors' conclusion:
'The dose-normalized C_{max} and AUC_{24h} of brexpiprazole on day 14 were higher in IM patients than in NM patients.'

Dose-corrected AUC_{24h} brexpiprazole compared to NM + gene dose 1/0:
IM: 239%</td>
</tr>
<tr>
<td>ref. 2
SmPC Rxulti (brexpiprazole) 18-08-20.</td>
<td>0

PM: A</td>
<td><u>Dose</u>:
Dosing modifications to half the recommended doses is required for patients with known CYP2D6 poor metaboliser status. Further dosing modifications to a quarter of the recommended dose is required for known CYP2D6 poor metabolisers while taking strong or moderate CYP3A4 inhibitors.
Table 1: Dose adjustments of Rxulti in patients who are CYP2D6 poor metabolisers and for concomitant use with CYP inhibitors
<table>
<tr><th>Factors</th><th>Adjusted dose</th></tr>
<tr><td colspan="2">CYP2D6 poor metabolisers</td></tr>
<tr><td>Known CYP2D6 poor meta-</td><td>Administer half of the recom-</td></tr>
</table></td>
<td></td>
</tr>
</table>

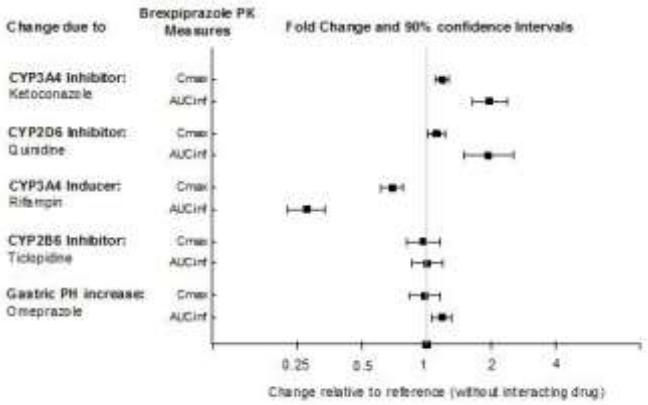
<table>
<tr>
<td>ref. 2, continuation</td>
<td></td>
<td>
<table>
<tr><td>bolisers</td><td>mended dose</td></tr>
<tr><td>Known CYP2D6 poor metabolisers taking strong/moderate CYP3A4 inhibitors</td><td>Administer a quarter of the recommended dose</td></tr>
<tr><td colspan="2">Patients taking CYP2D6 inhibitors and/or CYP3A4 inhibitors</td></tr>
<tr><td>Strong CYP2D6 inhibitors</td><td>Administer half of the recommended dose</td></tr>
<tr><td>Strong CYP3A4 inhibitors</td><td>Administer half of the recommended dose</td></tr>
<tr><td>Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors</td><td>Administer a quarter of the recommended dose</td></tr>
</table>
<u>Pharmacokinetics</u>:
Population pharmacokinetic evaluation shows that CYP2D6 poor metabolisers have 47% higher exposure to brexpiprazole compared to normal metabolisers.
<u>Interactions</u>:
Co-administration of a 2 mg single oral dose of brexpiprazole with quinidine (324 mg/day for 7 days), a potent inhibitor of CYP2D6, increased the AUC of brexpiprazole by 94% and no change in C_{max}.
Based on estimations from the population pharmacokinetic analysis, CYP2D6 normal metabolisers receiving both CYP3A4 and CYP2D6 inhibitors or CYP2D6 poor metabolisers receiving strong CYP3A4 inhibitors are expected to have approximately 4-5-fold increase in brexpiprazole concentrations and dose adjustment to a quarter of the dose is recommended for these subjects.
<u>Pharmacodynamics</u>:
Influences of genetic variation on the pharmacodynamic responses to brexpiprazole have not been investigated.
</td>
<td>Brexpiprazole exposure compared to NM:
PM: 147%

AUC brexpiprazole with strong CYP2D6 inhibitors versus without strong CYP2D6 inhibitors: 194%</td>
</tr>
<tr>
<td>ref. 3
EPAR Rxulti (brexpiprazole) 31-05-18.</td>
<td>0

IM: A
UM: A</td>
<td><u>Metabolism</u>:
In study 331-08-208, comparison of the AUC values in subjects in Group 4 (poor metabolizers of CYP2D6 isozyme) to the subjects in Groups 1 through 3 (normal metabolizers of CYP2D6 isozyme) indicates that brexpiprazole exposure was about two-fold higher in poor metabolizers of CYP2D6; however, no definitive information can be drawn from this study due to the limited number of subjects.
The effect of CYP2D6 poor metabolism has been further evaluated in a larger population and as a component of the population PK analysis. A 2-compartmental population PK model was developed for oral brexpiprazole. The population PK analysis was performed including a total of 2654 quantifiable brexpiprazole plasma concentrations from 154 healthy subjects and 3114 quantifiable plasma brexpiprazole concentrations from 1140 subjects with MDD and 5072 PK samples from 1247 schizophrenia subjects (2541 total subjects) were available for the population PK analysis. The evaluable dataset included 2357 subjects, who had at least one measurable brexpiprazole concentration. The effect of CYP2D6 metabolism status (poor, intermediate, and ultra-rapid relative to extensive) on CL/F was included as significant covariate in the final PopPK model (considering the inferred CYP2D6 metabolic status among subjects included in the popPK analysis, 3% were PM, 24% IM, 38.7% NM, 1.4% UR, and 33% were missing/inconclusive).
In subjects who are poor (PM), intermediate (IM) and ultra-rapid (UR) CYP2D6 metaboliser, CL/F was estimated to be -32%, -20% and +18%, respectively when compared to the value estimated for normal (NM) CYP2D6 metabolizer subjects, corresponding to a +47%, +25% and -21%, change in brexpiprazole exposure (AUC_{τ}), respectively. Dose</td>
<td>AUC brexpiprazole exposure compared to NM:
PM: 147-200%
IM: 125%</td>
</tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>PM: A</td>
<td>adjustment of half of the label-recommended maintenance dose is recommended in patients with poor CYP2D6 metabolism status and the necessity of a mandatory genotyping assay should be discussed by the applicant. The percentages of UR, NM, IM and PM are highly comparable among the three pivotal studies (331-10-002, 331-10-230 and 331-10-231).
Regarding population pharmacokinetic analysis, it is agreed that there is general agreement between the observed and predicted data, except where there is limited data i.e., for CYP2D6 poor and ultra-rapid metabolisers.
<u>Pharmacodynamics</u>:
The applicant has stated that no genetic effects on pharmacodynamics have been investigated. The CYP2D6 genetic differences are primarily a pharmacokinetic issue. This lack of data is not deemed critical, but the prescribers should be informed of it in the product information. As requested, the following statement “Influences of genetic variation on the pharmacodynamic responses to brexpiprazole have not been investigated” has been added to the section 5.1 of the SmPC under the subheading “Pharmacodynamic effects”.
<u>Adverse Events by Metabolizer Status</u>:
In fixed-dose schizophrenia trials there were only 16 subjects CYP2D6 poor metabolizers.
A comparison of the TEAEs from the 3 phase 3, fixed-dose schizophrenia trials showed that the incidence of subjects who received brexpiprazole 2 to 4 mg/day who reported ≥ 1 TEAE was 62.5% in CYP2D6 PM (10 of 16) and 60.5% in CYP2D6 NM (150 of 248). When evaluating individual TEAEs, there were no events that seemed to be predominantly or exclusively reported in PM subjects. The interpretation of this finding should be made with consideration for the small number of PM subjects overall (n = 16).
Although no clinically meaningful differences were observed with respect to the intrinsic factor of CYP2D6 metabolizer status (poor versus normal), a dose adjustment to one-half the maintenance dose is recommended in subjects with known CYP2D6 PM status to account for higher expected concentrations (up to 2-fold) in these subjects.</td>
<td>UM: 79%</td>
</tr>
<tr>
<td>ref. 4
SmPC Rexulti (brexpiprazole), USA, 17-06-20.</td>
<td>0

PM: A</td>
<td><u>Dose</u>:
Known CYP2D6 Poor Metabolizers: reduce the usual dosage by half.
Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers.
Table 1: Dosage adjustments of Rexulti for CYP2D6 Poor Metabolizers and for concomitant use with CYP3A4 and CYP2D6 inhibitors and/or CYP3A4 inducers
<table>
<tr><th>Factors</th><th>Adjusted Rexulti dosage</th></tr>
<tr><td colspan="2">CYP2D6 poor metabolisers</td></tr>
<tr><td>CYP2D6 poor metabolisers</td><td>Administer half of the usual dose</td></tr>
<tr><td>Known CYP2D6 poor metabolisers taking strong/moderate CYP3A4 inhibitors</td><td>Administer a quarter of the usual dose</td></tr>
<tr><td colspan="2">Patients taking CYP2D6 inhibitors and/or CYP3A4 inhibitors</td></tr>
<tr><td>Strong CYP2D6 inhibitors*</td><td>Administer half of the usual dose</td></tr>
<tr><td>Strong CYP3A4 inhibitors</td><td>Administer half of the usual dose</td></tr>
<tr><td>Strong/moderate CYP2D6 inhibitors with strong/mode-</td><td>Administer a quarter of the usual dose</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

ref. 4, continuation		rate CYP3A4 inhibitors **Patients taking CYP3A4 inducers** Strong CYP3A4 inducers: Double usual dose over 1 to 2 weeks. *In the clinical trials examining the adjunctive use of Rexulti in the treatment of major depressive disorder (MDD), dosage was not adjusted for strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine). Thus, CYP considerations are already factored into general dosing recommendations, and Rexulti may be administered without dosage adjustment in patients with MDD. Use in specific populations: Dosage adjustment is recommended in known CYP2D6 poor metabolizers, because these patients have higher brexpiprazole concentrations than normal metabolizers of CYP2D6. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers. Pharmacokinetics: Drug Interaction Studies Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when normal metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4. Figure 2: The effects of other drugs on brexpiprazole pharmacokinetics  	AUC brexpiprazole with strong CYP2D6 inhibitors versus without strong CYP2D6 inhibitors: approximately 200%

Risk group	IM with CYP2D6 inhibitor, IM and PM with strong CYP3A4 inhibitor, UM with CYP3A4 inducer

Comments:
-

Date of literature search: 13 July 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	0 A	yes	yes	13 September 2021
	IM	4 AA	yes	no	
	UM	0 A	yes	no	

Mechanism:
Brexpiprazole is mainly converted by CYP2D6 and CYP3A4 to the inactive metabolite DM-3411.
The NVZA does not indicate a therapeutic range for brexpiprazole, but in literature a therapeutic range of brexpiprazole of 40-140 ng/ml is mentioned with serum concentrations > 280 ng/ml considered to be toxic (Hiemke C et al.

Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018; 51:9-62).

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