CYP2C9: tolbutamide 1898 to 1904

*1 = no CYP2C9 gene variant, normal activity, *2 = CYP2C9 gene variant with decreased activity, *3 = CYP2C9 gene variant with strongly decreased activity, AUC = area under the concentration-time curve, Cl_{or} = oral clearance, IM = IM OTHER = intermediate metaboliser, other genotype (decreased CYP2C9 enzyme activity due to a gene variant with decreased activity other than *2 or *3), MR = metabolic ratio, NM = normal metaboliser (*1/*1) (normal CYP2C9 enzyme activity), NS = not significant, PM = PM OTHER = poor metaboliser, other genotype (strongly decreased CYP2C9 enzyme activity due to the presence of two gene variants with decreased activity, of which at least one other than *2 or *3), S = significant, $t_{1/2}$ = half-life, TOL = tolbutamide

Brief summary and justification of choices:
Tolbutamide is primarily metabolised by CYP2C9 to 4-hydroxytolbutamide. This inactive metabolite is then oxidised by dehydrogenases to carboxytolbutamide.
Only two studies found a significant clinical effect of gene variants leading to a reduced CYP2C9 activity. A study found a lower dose increase after the first prescription for 20 *1/*3+*2/*3, but not for 35 *1/*2+*2/*2 (Becker 2008). A study in healthy volunteers found an increased efficacy for *1/*3: the increase of plasma glucose concentration in 6 *1/*3 was half that in 12 *1/*1 after administration of 100 g glucose 1 hour after tolbutamide dosing (Shon 2002). Other studies did not find an effect on titrated dose (Swen 2010 (15 *1/*2+*2/*2, 14 *1/*3+*2/*3)) or (change in) plasma glucose concentration (Vormfelde 2009 (21 *1/*2, 16 *1/*3, 4 *2/*3, 3 *3/*3, Becker 2008 (13 *1/*2+*2/*2, 7 *1/*3+*2/*3), Chen 2005 (single dose, healthy volunteers; 9 *1/*3, 1 *3/*3), Lee 2003 (single dose, healthy volunteers; 5 *1/*2, 5 *1/*3), and Kirchheiner 2002 (single dose, healthy volunteers; 4 *1/*2, 3 *2/*2, 4 *1/*3, 3 *2/*3, 3 *3/*3)). Significant kinetic effects were found in all 7 studies (Vormfelde 2009 (for 16 *1/*3, 4 *2/*3, 3 *3/*3, not for 21 *1/*2), Chen 2005 (single dose, healthy volunteers; for 9 *1/*3, not for 1 *3/*3), Jetter 2004 (single dose, healthy volunteers; for 3 *1/*3, 1 *2/*2, not for 7 *1/*2)), Lee 2003 (single dose, healthy volunteers; 5 *1/*2, 5 *1/*3), Lee 2002 (single dose, healthy volunteers; 5 *1/*2, 5 *1/*3, 1 *2/*2), Shon 2002 (single dose, healthy volunteers; 6 *1/*3), and Kirchheiner 2002 (single dose, healthy volunteers; for 4 *1/*3, 3 *2/*3, 3 *3/*3, not for 4 *1/*2, 3 *2/*2)). Thus, although kinetic effects were found, clinical effects were scarce and indicate a positive effect, i.e. an increase in efficacy. For these reasons, the KNMP Pharmacogenetics Working Group concluded that therapy adjustment is not required for these gene-drug interactions (yes/no-interactions).
You can find a detailed overview of the observed kinetic and clinical effects in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr>
<td>ref. 1
Swen JJ et al.
Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus.
Pharmacogenomics 2010;11:1517-23.
PubMed PMID: 21121772.</td>
<td>3

*1/*3 + *2/*3: AA
*1/*2 + *2/*2: AA</td>
<td>64 patients started tolbutamide therapy. 30% of these patients used metformin.
The stable tolbutamide dose was defined as the dose on the first period of 270 consecutive days or more without tolbutamide dose adjustment, or initiation or adjustment of therapy with another sulfonylurea, insulin or metformin.
Relevant co-medication was not excluded.
120 patients were calculated to be needed for a power of at least 80%.

Genotyping:
- 35x *1/*1
- 15x *1/*2+*2/*2
- 14x *1/*3+*2/*3

Results:
<table>
<tr><td colspan="2">Stable daily dose compared to *1/*1 (900 mg):</td></tr>
<tr><td>*1/*3+*2/*3</td><td>NS</td></tr>
<tr><td>*1/*2+*2/*2</td><td>NS</td></tr>
</table>
NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Dutch patient group.</td>
<td>Authors’ conclusion: ‘Genotyping for the CYP2C9*2 and CYP2C9*3 alleles currently appears to have no clinical implications for dosing of sulfonylureas in primary care patients with Type 2 diabetes mellitus.’</td>
</tr>
</table>

ref. 2 Vormfelde SV et al. Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers. Clin Pharmacol Ther 2009;86:54-61.	3 *1/*2: AA *1/*3: A *2/*3: A *3/*3: A	130 healthy volunteers, 86x *1/*1, 21x *1/*2, 16x *1/*3, 4x *2/*3, 3x *3/*3, received a single dose of 500 mg tolbutamide, no co-medication; *kinetic endpoints* *1/*2 versus *1/*1: - decrease in Cl_{or} from 0.78 to 0.74 L/h (NS by 5%) - increase in $t_{1/2}$ from 8.01 to 8.82 h (S for the trend, by 10%) *1/*3 versus *1/*1: - decrease in Cl_{or} from 0.78 to 0.52 L/h (S for the trend, by 33%) - increase in $t_{1/2}$ from 8.01 to 11.65 h (S for the trend, by 45%) *2/*3 versus *1/*1: - decrease in Cl_{or} from 0.78 to 0.4 L/h (S for the trend, by 49%) - increase in $t_{1/2}$ from 8.01 to 15.14 h (S for the trend, by 89%) *3/*3 versus *1/*1: - decrease in Cl_{or} from 0.78 to 0.13 L/h (S for the trend, by 83%) - increase in $t_{1/2}$ from 8.01 to 45.99 h (S for the trend, by 474%) *clinical endpoints* No significant difference in glucose concentration after 0.5 and 4 hours between the different genotypes (intake of approx. 20 g carbohydrates after 0.5 and 2 hours).	
ref. 3 Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.	4 *1/*2 + *2/*2: AA *1/*3 + *2/*3: A	296 patients received tolbutamide average initial dose 613 mg/day. A subgroup of 172 patients, 117x *1/*1, 35x (*1/*2 + *2/*2), 20x (*1/*3 + *2/*3) received $\geq$ 10 prescriptions. For a subgroup of 65 patients, 45x *1/*1, 13x (*1/*2 + *2/*2), 7x (*1/*3 + *2/*3), the change in glucose concentration was determined 180 days after start of treatment. Changes are corrected for age and gender. (*1/*2 + *2/*2) versus *1/*1: - dose increase between the 1st and 10th prescription is 14 mg/day lower than for *1/*1 (NS) - difference in prescribed daily dose between prescription 6-20 and prescription 1 is 27 mg/day lower than for *1/*1 (NS) - increased change in glucose concentration: extra decrease of -0.28 mmol/L versus *1/*1 (NS) (*1/*3 + *2/*3) versus *1/*1: - dose increase between the 1st and 10th prescription is 269 mg/day lower than for *1/*1 (S) - difference in prescribed daily dose between prescription 6-20 and prescription 1 is 316 mg/day lower than for *1/*1 (S) - increased change in glucose concentration: extra decrease of -1.24 mmol/L versus *1/*1 (NS)	Authors' conclusion: "Patients with diabetes mellitus who are carriers of a CYP-2C9*3 allele require lower doses of tolbutamide to regulate their serum glucose levels compared to patients with the wild-type genotype. This knowledge is clinically important, because it may mean that such patients have a higher risk of hypoglycemia after starting treatment according to a standard dose scheme."
ref. 4 Chen K et al. Relationship of P450 2C9 genetic	3	20 Chinese healthy volunteers, 10x *1/*1, 9x *1/*3, 1x *3/*3, received a single dose of 500 mg tolbutamide, no co-medication;	

polymorphisms in Chinese and the pharmacokinetics of tolbutamide. J Clin Pharm Ther 2005;30:241-9. **ref. 4, continuation**	*1/*3: A *3/*3: AA	*kinetic endpoints* - *1/*3: increase in the AUC versus *1/*1 from 2025 to 3475.5 µM/h (S by 72%), increase in $t_{1/2}$ from 7.1 to 13.9 h (S by 96%). - *3/*3: increase in the AUC versus *1/*1 from 2025 to 9654.2 µM/h (by 377%), increase in $t_{1/2}$ from 7.1 to 79.4 h. *clinical endpoints* - *1/*3: no sign. difference versus *1/*1 in decrease in the AUC blood glucose, for 0-3 hr from -3.0 to -1.7 µM.h, for 0-24 hr from 11.6 to 3.6 µM.h. The serum glucose concentration is significantly higher after 9 and 12 hours. - *3/*3: decrease in the AUC blood glucose versus *1/*1, for 0-3 hr from -3.0 to -3.7 µM.h and for 0-24 hr from 11.6 to -13.7 µM.h.	
ref. 5 Jetter A et al. Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. Eur J Clin Pharmacol 2004;60:165-71.	3 *1/*2: AA *1/*3: A *2/*2: A	26 Caucasian healthy volunteers, 15x *1/*1, 7x *1/*2, 3x *1/*3, 1x *2/*2, received a single dose of 125 mg tolbutamide, no co-medication; All results compared to *1/*1 - *1/*2: no sign. change in any of the kinetic parameters. - *1/*3: non-significant increase in $t_{1/2}$, other parameters changed significantly, increase in the AUC from 149 to 208 µg/mL.h (S by 40%), decrease in Cl_{or} from 0.85 to 0.60 L/hour (S by 29%). - *2/*2: increase in $t_{1/2}$ from 7.5 to 10.7 hours, increase in the AUC from 149 to 219 µg/mL.h (S by 47%), decrease in Cl_{or} from 0.85 to 0.57 L/h (S by 33%).	
ref. 6 Lee CR et al. Tolbutamide, flurbiprofen, and losartan as probes of CYP-2C9 activity in humans. J Clin Pharmacol 2003;43:84-91.	3 *1/*2: A *1/*3: A	15 healthy volunteers, 5x *1/*1, 5x *1/*2, 5x *1/*3, received a single dose of 500 mg tolbutamide, no co-medication; *kinetic endpoints* - *1/*2: increase in the AUC versus *1/*1 from 560.9 to 815.3 µg.h/mL (S by 45%), decrease in Cl_{or} from 15 to 10.6 mL/min (S by 29%), non-significant increase in $t_{1/2}$. - *1/*3: increase in the AUC versus *1/*1 from 560.9 to 1078.9 µg.h/mL (S by 92%), decrease in Cl_{or} from 15 to 7.8 mL/min (S by 48%), increase in $t_{1/2}$ from 7.1 to 13.2 hours (S by 86%). *clinical endpoints* No significant difference in blood glucose between the genotypes before and after administration of tolbutamide.	
ref. 7 Lee CR et al. Evaluation of cytochrome P4502C9 metabolic activity with tolbutamide in CYP2C91 heterozygotes. Clin Pharmacol Ther 2002;72:562-71.	3 *1/*2: A *1/*3: A *2/*2: A	16 healthy volunteers, 5x *1/*1, 5x *1/*2, 5x *1/*3, 1x *2/*2, received a single dose of 500 mg tolbutamide, no co-medication; Cl_{form} measured = quantity of metabolite excreted in urine/ plasma AUC in 24 hr. - *1/*2: decrease in Cl_{form} versus *1/*1 from 17.1 to 11.6 mL/min (S by 32%). - *1/*3: decrease in Cl_{form} versus *1/*1 from 17.1 to 9.9 mL/min (S by 42%). - *2/*2: decrease in Cl_{form} versus *1/*1 from 17.1 to 13.9 mL/min (by 19%).	
ref. 8 Shon JH et al. Effects of CYP2C19 and CYP2C9 genetic polymorphisms on the disposition of	3	18 healthy Korean volunteers, 12x *1/*1, 6x *1/*3, received a single dose of 500 mg tolbutamide, no co-medication; *kinetic endpoints* - *1/*3: increase in the AUC versus *1/*1 + 2C19NM from 656.2 to 1241.7 µg/mL.h (S by 89%), decrease in Cl_{or} from	

and blood glucose lowering response to tolbutamide in humans. Pharmacogenetics 2002;12:111-9. **ref. 8, continuation**	*1/*3: AA[#]	12.1 to 8.9 mL/h/kg (S by 26%), increase in $t_{1/2}$ from 6.7 to 11.6 hours (S by 73%). Increase in ratio AUC TOL/4-OH-TOL from 63.5 to 347.7 (S by 448%). *clinical endpoints* Glucose tolerance test using 100 g glucose 1 hour after administration of tolbutamide: serum glucose concentration exhibits a significant lower increase for *1/*3 than for *1/*1, 22.0 versus 44.5 mg/dL (S by 51%), the AUC of the difference in glucose concentration is also significantly lower for *1/*3 than for *1/*1, 25.4 versus 71.2 mg/dL.h (S by 180%). N.B.: no pharmacokinetic or pharmacodynamic differences between CYP2C19 NMs and PMs	
ref. 9 Kirchheiner J et al. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. Pharmacogenetics 2002;12:101-9.	3 *1/*2, *2/*2: AA *1/*3, *2/*3, *3/*3: A	23 healthy volunteers, 6x *1/*1, 4x *1/*2, 3x *2/*2, 4x *1/*3, 3x *2/*3, 3x *3/*3, received a single dose of 500 mg tolbutamide, no co-medication; *kinetic endpoints, all versus *1/*1* - *1/*2: decreased Cl_{or} from 0.97 to 0.86 (NS by 11%). - *2/*2: decreased Cl_{or} from 0.97 to 0.75 (NS by 23%). - *1/*3: decreased Cl_{or} from 0.97 to 0.56 (S by 42%) - *2/*3: decreased Cl_{or} from 0.97 to 0.45 (S by 54%) - *3/*3: decreased Cl_{or} from 0.97 to 0.15 (S by 85%) *clinical endpoints* No difference in insulin and glucose tolerance (after administration of 3x 75 g glucose) between the various genotypes	Authors' conclusion: 'Although insulin and glucose did not correspond to this difference in clearance, it might be speculated that dose adjustment nevertheless may result in a reduction of adverse events or drug interactions in patients.'

Risk group	--

Comments:
- For the period after 2009 only studies with clinical outcomes in patients were included. Other studies did not add enough to the evidence.
- Kirchheiner et al. [Clin Pharmacokinet. 2005;44:1209-1225] state in the discussion of the therapeutic consequences of pharmacogenetic variability for oral anti-diabetics that: "the relationship between plasma sulphonylurea concentrations and antihyperglycaemic effects measured as insulin response and blood glucose has high interindividual variability and was even reported to be bell-shaped, making predictions of pharmacodynamic consequences from the plasma drug concentrations difficult. In addition, downregulation of ß-cell sensitivity was found during long-term sulphonylurea treatment. This again explains why genotype-dependent effects in pharmacokinetics are not automatically reflected, to a similar extent, in antihyperglycaemic effects. Particularly during long-term treatment with sulphonylurea drugs, daily dosages might range in the upper end of the dose-response curve where changes in drug tissue concentrations may not play a role in the antihyperglycaemic effects. In contrast, at the initiation of drug treatment, particularly for the choice of the starting dose, genotyping might help in preventing overdose in patients with CYP2C9 genotypes predicting low activity."

Date of literature search: 30 January 2023.

	Genotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	*1/*2	3 A	Yes	No	16 May 2023
	*1/*3	3 AA[#]	Yes	No	
	*2/*2	3 A	Yes	No	
	*2/*3	3 A	Yes	No	
	*3/*3	3 A	Yes	No	
	IM	--	Yes	No	
	PM	--	Yes	No	

Mechanism:
Tolbutamide is primarily metabolised by CYP2C9 to 4-hydroxytolbutamide. This inactive metabolite is then oxidised by dehydrogenases to carboxytolbutamide.