CYP2C9: glibenclamide 1877 to 1883

*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, $AUEC_{glucose}$ = incremental area under glucose concentration-time curve, $AUEC_{insulin}$ = incremental area under insulin concentration-time curve, Cl_{or} = oral clearance, HbA_{1c} = glycated haemoglobin, 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, OR = odds ratio, OR_{adj} = adjusted odds ratio, 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, t½ = half-life.

Brief summary and justification of choices:
Glibenclamide is primarily metabolised by CYP2C9 to 4-trans-hydroxyglibenclamide and 3-cis-hydroxyglibenclamide. These metabolites have a very weak effectiveness. Glibenclamide inhibits CYP2C9 and thereby its own metabolism. An effect on glibenclamide exposure was observed for *1/*3 and *3/*3 (Yin 2005 (6x *1/*3), Niemi 2002 (2x *1/*3), and Kirchheiner 2002 (3x *3/*3)). In patients and healthy volunteers. *1/*3 and *3/*3 have been shown to enhance efficacy (Castelán-Martínez 2018 (26x *1/*3), Surendiran 2011 (15x *1/*3), Yin 2005 (6x *1/*3), and Kirchheiner 2002 (3x *3/*3)). A significant increase in hypoglycaemic response was not observed (Surendiran 2011 (15x *1/*3), Holstein 2005 (3 glibenclamide users with severe hypoglycaemia and 59 controls), and Yin 2005 (6x *1/*3)). However, because ineffectiveness is a greater problem with glibenclamide than hypoglycaemia, effectiveness is the most relevant outcome. No kinetic and clinical effects have been found for *1/*2 (Castelán-Martínez 2018 (38x *1/*2), Becker 2008 (8x (*1/*2 + *2/*2)), Niemi 2002 (3x *1/*2), and Kirchheiner 2002 (4x *1/*2)), *2/*2 (Castelán-Martínez 2018 (2x *2/*2), Becker 2008 (8x (*1/*2 + *2/*2)), and Kirchheiner 2002 (3x *2/*2)), *2/*3 (Becker 2008 (6x (*1/*3 + *2/*3)), Holstein 2005 (62 glibenclamide users), and Kirchheiner 2002 (3x *2/*3)), IM OTHER (no studies), and PM OTHER (no studies).
Because of the observed kinetic and clinical effects, the KNMP Pharmacogenetics Working Group concludes that there is a CYP2C9-glibenclamide interaction. However, because only positive clinical effects were observed, the KNMP Pharmacogenetics Working Group decided that there is no need for action (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 in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

Source	Code	Effect	Comments
ref. 1 Castelán-Martínez OD et al. CYP2C9*3 gene variant contributes independently to glycaemic control in patients with type 2 diabetes treated with glibenclamide. J Clin Pharm Ther 2018;43:768-74. PMID: 29802808.	3	404 patients were treated with glibenclamide (median dose 10 mg/day (range 2.5-30 mg/day)), 60% in combination with metformin. Good glycaemic control was defined as HbA_{1c} levels ≤ 53 mmol/mol (7%). Poor glycaemic control was defined as HbA_{1c} levels ≥ 64 mmol/mol (8%). Patients with HbA_{1c} levels between 53 and 64 mmol/mol were excluded from the study 42% of the patients had good glycaemic control. Treatment with glucose-lowering drugs other than glibenclamide and metformin was excluded. Co-medication with effect on CYP2C9 was not excluded. Association analysis was by multiple logistic regression adjusting for age, exercise, body mass index, glibenclamide dose, time with type 2 diabetes, concomitant metformin and metformin dose. The power of the study was calculated to be 99%, based on a sample size of 404 patients, a good glycaemic control in 30% of patients, a CYP2C9*3 frequency of 5% and a genetic effect size of 2.74. Genotyping:	Authors' conclusion: 'The findings suggest that CYP2C9*3 genetic variant independently contributes to good glycaemic control of patients with type 2 diabetes treated with glibenclamide.'

<table>
<tr>
<td>ref. 1, continuation</td>
<td>*1/*2: AA
*1/*2 + *2/*2: AA

*1/*3: AA#</td>
<td>
*2:
- 364x no *2
- 38x *2-heterozygous
- 2x *2/*2

*3:
- 378x no *3
- 26x *3-heterozygous

<table>
<tr><td colspan="4">Percentage of patients with good glycaemic control compared to no *2 or no *3:</td></tr>
<tr><td colspan="2"></td><td>OR_{adj} (95% CI)</td><td>value for no *2 or no *3</td></tr>
<tr><td colspan="2">*2-heterozygous</td><td>NS</td><td rowspan="2">42%</td></tr>
<tr><td colspan="2">*2-heterozygous + *2/*2</td><td>NS</td></tr>
<tr><td rowspan="3">*3-heterozygous</td><td>all</td><td>2.78 (1.14-6.76) (S)</td><td>41%</td></tr>
<tr><td>only glibenclamide</td><td>6.63 (1.61-27.29) (S)</td><td></td></tr>
<tr><td>glibenclamide + metformin</td><td>NS</td><td></td></tr>
</table>

NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Mexican population.
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<td>ref. 2
Surendiran A et al. Influence of CYP-2C9 gene polymorphisms on response to glibenclamide in type 2 diabetes mellitus patients. Eur J Clin Pharmacol 2011;67:797-801. PubMed PMID: 21336994.</td>
<td>3

*1/*3 + *1/*2: AA#</td>
<td>
80 patients were treated with glibenclamide for more than 3 months, 98% in combination with metformin.
Glibenclamide plasma concentrations were determined 2.5 hours after dosing (peak concentrations).
The severity of the hypoglycaemic adverse events was defined as the mean number of hypoglycaemic adverse events per week multiplied by the severity score, given as mild (score 1), moderate (score 2), and severe (score 3).
Controlled diabetes was defined as fasting plasma glucose values of < 6.1 mmol/L.
Relevant co-medication was not excluded.

Genotyping:
- 64x *1/*1
- 1x *1/*2
- 15x *1/*3

Results:
<table>
<tr><td colspan="3">Results compared to *1/*1:</td></tr>
<tr><td></td><td>*1/*3 + *1/*2</td><td>value for *1/*1</td></tr>
<tr><td>% of patients with controlled diabetes</td><td>x 2.0 (S)</td><td>25%</td></tr>
<tr><td>median weekly number of hypoglaecemic events</td><td>NS</td><td>1</td></tr>
<tr><td>median weekly number of hypoglaecemic events multiplied by the severity score</td><td>NS</td><td>2</td></tr>
<tr><td>median dose and body weight corrected glibenclamide peak plasma concentrations</td><td>x 1.8 (NS)</td><td>1.539 ng.kg.day/ml.mg</td></tr>
</table>

NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this South Indian Tamilian patient group.
</td>
<td>Authors' conclusion: 'The type 2 diabetes mellitus patients participating in this study with variant genotypes of CYP-2C9 were found to respond better to treatment with glibenclamide than those with the normal genotype. The variant genotype CYP2C9 *1/*3 did not significantly influence the hypoglycemic adverse effects among those patients on long-term glibenclamide treatment.'</td>
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<td>ref. 3
Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the</td>
<td>4</td>
<td>34 patients, 20x *1/*1, 8x (*1/*2 + *2/*2), 6x (*1/*3 + *2/*3) received ≥ 10 prescriptions for glibenclamide, mean initial dose 6.1 mg/day.

(*1/*2 + *2/*2) versus *1/*1:</td>
<td>Authors' conclusion: "As the number of users of the non-tolbutamide sulfonylurea is small, it is</td>
</tr>
</table>

dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.	*1/*2 + *2/*2: AA *1/*3 + *2/*3: AA	- dose increase between the 1st and 10th prescription is 2.0 mg/day lower than for *1/*1 (NS) (*1/*3 + *2/*3) versus *1/*1: - dose increase between the 1st and 10th prescription is 1.3 mg/day lower than for *1/*1 (NS)	likely that these numbers are too small to detect differences for these drugs in this study. This is demonstrated by the post hoc power analysis."
ref. 4 Yin OQ et al. CYP2C9, but not CYP2C19, polymorphisms affect the pharmacokinetics and pharmacodynamics of glyburide in Chinese subjects. Clin Pharmacol Ther 2005;78:370-7.	3 *1/*3: AA#	18 Chinese healthy volunteers, of which 12 are CYP2C19 NM: 6x CYP2C9*1/*1, 6x CYP2C9*1/*3, single dose of 5 mg glibenclamide, no co-medication, standardised meals after 3 and 10 hours. *1/*3 versus *1/*1: - increase in AUC from 457 ng.h/mL to 1028 ng.h/mL (S by 125%) - decrease in Cl_{or} from 2.98 mL/min.kg to 1.49 mL/min.kg (S by 49.9%) - increase in t½ from 2.09 h to 3.58 h (S by 71%) - greater blood glucose reduction after 2 hours: 41.8% versus 24.0% (initial concentration of 5.27 mmol/L and 4.96 mmol/L resp.) (S) - greater increase in insulin after 2 hours: 319% versus 158% (initial concentration of 41.14 pmol/L and 52.87 pmol/L resp.) (NS) - hypoglycaemia in 3 of the 6 versus 1 of the 6 individuals (significance unknown)	Authors' conclusion: "CYP2C9, but not CYP2C19, polymorphism appears to exert a dominant influence on glyburide pharmacokinetics and pharmacodynamics in vivo. Further studies in diabetic patients with long-term dosing are warranted to confirm these findings."
ref. 5 Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol ;60:103-6.	3 *3/*3 + *2/*3: AA	20 diabetes patients with severe hypoglycaemia, 3x glibenclamide, 17x glimepiride. Control group 1: A total of 337 diabetes patients with no history of hypoglycaemia, 59x glibenclamide (average dose lower than in the hypoglycaemia group), 278x other oral glucose-lowering products, including glimepiride; co-medication unknown. Determine frequency of CYP2C9 genotypes in both groups. Result: - *3/*3 and *2/*3 are more common in the hypoglycaemia group than in the control group: 10% versus 2%, OR = 5.2 (S) - the patients with *3/*3 and *2/*3 in the hypoglycaemia group were using glimepiride.	Authors' conclusion: "These findings suggest that among other factors, individuals with genetically determined low CYP2C9 activity are at an increased risk of sulphonylurea-associated severe hypoglycaemia. Thus, genotyping might be a tool for the better prediction of adverse effects caused by oral hypoglycaemic agents."
ref. 6 Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.	3 *1/*3: A *1/*2: AA	A total of 29 healthy volunteers, of which 10 received glibenclamide: 5x *1/*1, 3x *1/*2, 2x *1/*3, single dose of 1.75 mg glibenclamide, standardised meals after 15 min. and 3 hours. *1/*3 versus *1/*1: - increase in AUC from 224 ng.h/mL to 627 ng.h/mL (S by 180%) - increase in t½ from 1.7 h to 2.6 h (S by 48%) - difference in blood glucose response is non-significant. *1/*2 versus *1/*1: - no significant differences	Authors' conclusion: "Genetic polymorphisms of CYP2C9 markedly affect the pharmacokinetics of glyburide. The influence of the CYP2C9 *3 variant allele on glyburide pharmacokinetics may be clinically significant." "Hence, to reduce the risk of hypoglycemia at the initiation of sulfonylurea therapy, the starting dose of glyburide should probably be

ref. 6, continuation			about half of the normal dose in patients heterozygous for the CYP2C9*3 allele. In patients homozygous for CYP2C9*3, considerably lower doses should be used."
ref. 7 Kirchheiner J et al. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. Clin Pharmacol Ther 2002;71:286-96.	3 *2/*2: AA *3/*3: A *1/*2: AA *1/*3: AA *2/*3: AA	A total of 21 healthy volunteers, 4x *1/*1, 4x *1/*2, 3x *2/*2, 4x *1/*3, 3x *2/*3, 3x *3/*3, single dose of 3.5 mg glibenclamide, 75 g glucose after 1, 4.5 and 8 hours, no caffeine. Cl_{or} versus *1/*1: - *2/*2: 90% (NS) - *3/*3: 50% (S) Total insulin secretion in 12 hours (estimated insulin V = 25 L): - *1/*1: 29 IU - *3/*3: 36 IU (S) Average maximum concentration of plasma-insulin: higher for *3/*3 (S) Glucose AUC_{0-12}: differences between genotypes are NS. No significant differences were found for *1/*2, *1/*3 and *2/*3 compared to *1/*1 for Cl_{or}, t½ and total insulin secretion in 12 hours. N.B. This article is difficult to interpret, as results obtained from a population-pharmacokinetic-pharmacodynamic model and measured values were used interchangeably.	Authors' conclusion: "Carriers of the CYP2C9 variant *3 had decreased oral clearances of glyburide. Corresponding differences in insulin plasma levels indicated that dose adjustment based on CYP2C9 genotype may improve antidiabetic treatment."

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."
- Yin, 2005 found that the glibenclamide "exposure" (AUC_{0-2hr}) for individuals correlated well to the glucose response ($AUEC_{0-2,\ glucose}$) and the change in insulin ($AUEC_{0-2,\ insulin}$) (S).

Date of literature search: 13 January 2023.

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

	IM	-	Yes	No	
	PM	-	Yes	No	

Mechanism:
Glibenclamide is primarily metabolised by CYP2C9 to 4-trans-hydroxyglibenclamide and 3-cis-hydroxyglibenclamide. These metabolites have a very weak effectiveness. Glibenclamide inhibits CYP2C9 and thereby its own metabolism.