CYP2C9: glimepiride 1891 to 1897

*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, 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:
Glimepiride is metabolised to weakly effective hydroxy glimepiride by CYP2C9. This metabolite is then converted by dehydrogenases to an inactive carboxy metabolite.
Three studies demonstrated a significant clinical effect of gene variants leading to a reduced CYP2C9 activity (Bhatt 2014 (1x *1/*2, 3x *1/*3), Suzuki 2006 (2x *1/*3), and **Holstein** 2005 (20 patients with severe hypoglycaemia, among whom 17 glimepiride users, compared to a control group without hypoglycaemia)). In two studies, this effect was an improvement in the clinical effectiveness for *1/*3 (stronger decrease of HbA_{1c} in Suzuki 2006 and a larger decrease in postprandial plasma glucose concentration during treatment in Bhatt 2014). Holstein 2005 found an increased risk of hypoglycaemia for *2/*3+*3/*3, but not for *1/*2 and for *1/*3. Two other studies did not find an increased risk for *1/*2 and/or *1/*3 either (Gökalp 2011 (24x *1/*2+*1/*3) and Ragia 2009 (80 patients with and 74 without glimepiride-induced hypoglycaemia)). Three studies found no effect of CYP2C9 gene variants on the titrated glimepiride dose (Swen 2010 (10x *1/*2+*2/*2, 9x *1/*3+*2/*3), Ragia 2009 (39x *1/*2, 10x *1/*3), and Becker 2008 (12x *1/*2+*2/*2, 3x *1/*3+*2/*3)).
Two studies in healthy volunteers found an increase in AUC for *1/*3 or *1/*3+*2/*3, but not for *1/*2 (Wang 2005 (9x *1/*3, 1x *3/*3) and Niemi 2002 (5x *1/*2, 2x *1/*3, 1x *2/*3)).
As a lack of effectiveness is a much more common problem with sulphonyl urea derivatives than the occurrence of hypoglycaemia, the KNMP Pharmacogenetics Working Group decided that the favourable effect on effectiveness is more important than the unfavourable effect on the risk of hypoglycaemia. Therefore, no action is recommended 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 in 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
Bhatt D et al.
Investigating the role of plasma glucose concentration as a phenotypic marker for CYP2C9 genetic variants, in the diabetic population of Gujarat.
Indian J Pharm Sci 2014;76:72-7.
PubMed PMID: 24799741.</td><td>3

*1/*3: AA#
*1/*2: AA</td><td>30 patients were treated with glimepiride with or without metformin,
The postprandial plasma glucose concentrations before and after treatment were compared.
Co-medication with influence on CYP2C9 activity was excluded, but there was no correction for treatment with or without metformin.

Genotyping:
- 26x *1/*1
- 1x *1/*2
- 3x *1/*3

Results:
<table><tr><td colspan="2">Decrease in postprandial plasma glucose concentration during treatment per mg of glimepiride compared to *1/*1 (approximate value 2 mmol/L):</td></tr><tr><td>*1/*3</td><td>x 3.5 (S)</td></tr><tr><td>*1/*2</td><td>x 6</td></tr></table></td><td>Authors’ conclusion: ‘Patients with CYP-2C9*1/*3 genotype showed greater mean glucose drop per milligram of drug values than patients with CYP2C9*1/*1 wild-type genotype for both glipizide and glimepiride.’</td></tr>
</table>

<table>
<tr><td>ref. 1, continuation</td><td></td><td>NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Indian patient group.</td><td></td></tr>
<tr><td>ref. 2
Gökalp O et al.
Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP-2C8 polymorphisms in routine clinical setting.
Eur J Clin Pharmacol
2011;67:1223-9.
PubMed PMID:
21691805.</td><td>3

*1/*2 +
*1/*3: AA</td><td>50 patients were treated with glimepiride for 3 months or longer. 76% of patients was also treated with other antidiabetics. 6 patients (12%) reported hypoglycaemia. None of these patients needed hospitalisation.
Hypoglycaemia was defined by symptoms of sweating, tremor, anxiety and/or palpitations and confirmed by home capillary blood glucose determinations showing values < 3.9 mmol/L and response to sugar intake. Occurrence was assessed during a 3-month period.
Co-medication with CYP2C9 substrates, inhibitors or indu--cers was not excluded.

Genotyping:
- 26x *1/*1
- 24x *1/*2+*1/*3

Results:<table><tr><td colspan="2">Percentage of patients with hypoglycaemia compared to *1/*1 (7.7% of patients with hypoglycaemia):</td></tr><tr><td>*1/*2+*1/*3</td><td>NS</td></tr></table>
NOTE: Genotyping was for *2 and *3. These are the most important gene variant in this Turkish patient group.</td><td>Authors' conclusion: 'However, only in the gliclazide group a significant association between CYP2C9 genotype and hypoglycaemic attacks was observed.'</td></tr>
<tr><td>ref. 3
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>59 patients started glimepiride therapy. 30% of these patients used metformin.
The stable glimepiride dose was defined as the dose on the first period of 270 consecutive days or more without glimepiride 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:
- 40x *1/*1
- 10x *1/*2+*2/*2
- 9x *1/*3+*2/*3

Results:<table><tr><td colspan="2">Stable daily dose compared to *1/*1 (2.02 mg):</td></tr><tr><td>*1/*3+*2/*3</td><td>NS, trend for a decrease (p = 0.07)</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 variant 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>
<tr><td>ref. 4
Ragia G et al.
Presence of CYP-2C9*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas.
Pharmacogenomics 2009;10:1781-7.</td><td>4

*1/*3: AA

*1/*2: AA</td><td>Case-control study involving 80 diabetes patients with glimepiride-induced hypoglycaemia, 46x *1/*1, 24x *1/*2, 9x *1/*3, 1x *2/*3, and 74 patients without glimepiride-induced hypoglycaemia, 57x *1/*1, 15x *1/*2, 1x *1/*3, 1x *2/*2; no CYP-2C9 inhibitors, similar distribution of anti-hypertensive medication that can mask symptoms of hypoglycaemia across the groups.

Cases versus controls:
- increase in the frequency of *1/*3 by a factor 8, from 1.4% to 11.3% (NS)
- increase in the frequency of *1/*2 by a factor 1.5, from 20% to 30% (NS)
- no difference in average dose of glimepiride (both 5.12</td><td>Authors' conclusion: "In type 2 diabetic patients, CYP2C9*3 increases the risk of hypoglycaemia when they are treated with sulfonylureas, possibly due to impaired metabolism of these drugs. CYP2C9 genotyping might thus be a useful tool for predicting adverse effects caused by sulfonylureas</td></tr>
</table>

ref. 4, continuation		mg/day) Dose versus *1/*1 for both groups combined: - no significant decrease in dose for *1/*2 and for *1/*3 (NS) The total study group (cases: 80x glimepiride, 12x gliclazide) exhibited a significant increase in the frequency of *1/*3, but not of *1/*2, in the case group versus the control group. NOTE: significance has not been determined separately for glimepiride.	and help clinicians in safer prescribing of oral hypoglycaemic agents."
ref. 5 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: AA	42 patients, 27x *1/*1, 12x (*1/*2 + *2/*2), 3x (*1/*3 + *2/*3) received ≥ 10 prescriptions for glimepiride, ave. initial dose 1.38 mg/day. (*1/*2 + *2/*2) versus *1/*1: - dose increase between the 1st and 10th prescription is 0.07 mg/day lower than for *1/*1 (NS) (*1/*3 + *2/*3) versus *1/*1: - dose increase between the 1st and 10th prescription is 1.1 mg/day higher than for *1/*1 (NS)	Authors' conclusion: "As the number of users of the non-tolbutamide sulfonylurea is small, it is 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. 6 Suzuki K et al. Effect of CYP2C9 genetic polymorphisms on the efficacy and pharmacokinetics of glimepiride in subjects with type 2 diabetes. Diabetes Res Clin Pract 2006;72:148-54.	4 *1/*3:AA#	134 Japanese diabetes patients, 132x *1/*1, 2x *1/*3, glimepiride 1 mg/day for six months, no co-medication, no liver function abnormalities. Comparison of 40x*1/*1 to 2x *1/*3: - *1/*3: decrease in HbA_{1c} concentration after six months: greater than in *1/*1 (S). - two *1/*3 patients responded well to glimepiride during the first phase of the treatment Pharmacokinetic study, 4x *1/*1, 2x *1/*3, single dose of glimepiride 1 mg after a meal. *1/*3 versus *1/*1: - increase in AUC by 161%, from 292 ng.h/mL to 763 ng.h/mL (S) - decrease in Cl_{or} by 64% from 3.78 to 1.35 L/h (S)	Authors' conclusion: "These results suggested that the lower hydroxylation activity of glimepiride in the subject with type 2 diabetes and CYP2C9*1/*3 led to a marked elevation in the plasma concentrations of glimepiride and a stronger pharmacological effect of glimepiride."
ref. 7 Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.	3 *3/*3 + *2/*3: D *1/*2: AA *1/*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, 56x glimepiride (average dose equal to the hypoglycaemia group), 281x other oral glucose-lowering products, including glibenclamide; 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 and no co-medication. - neither *1/*2 nor *1/*3 is more common in the hypoglycaemia group than in the control group (NS).	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. 8 Wang R et al. Pharmacokinetics of	3	19 healthy volunteers, 9x *1/*1, 9x *1/*3, 1x *3/*3, single dose of 4 mg glimepiride.	Authors' conclusion: "CYP2C9 genotype significantly affected

glimepiride and cytochrome P450 2C9 genetic polymorphisms. Clin Pharmacol Ther 2005;78:90-2. **ref. 8, continuation**	*1/*3: A *3/*3: AA	*1/*3 versus *1/*1: - increase in AUC from 1462 µg.h/L to 1878 µg.h/L (S by 30%) - increase in t½ from 11.4 h to 18.6 h (S by 63%) - decrease in Cl_{or} from 3.0 L/h to 2.3 L/h (S by 25%) *3/*3 versus *1/*1: - increase in AUC from 1462 µg.h/L to 2248 µg.h/L (NS by 50%) - increase in t½ from 11.4 h to 38.2 h (NS by 235%) - decrease in Cl_{or} from 3.0 L/h to 1.8 L/h (NS by 40%) - differences in blood glucose variables are NS	the pharmacokinetics of glimepiride."
ref. 9 Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.	3 *1/*3 + *2/*3: A *1/*2: AA	29 healthy volunteers, of which 20 received glimepiride:12x *1/*1, 5x *1/*2, 2x *1/*3, 1x *2/*3, single dose of 0.5 mg glimepiride, standardised meals after 15 min. and 3 hours. (*1/*3 + *2/*3) versus *1/*1: - increase in AUC by 167%, from 116 ng.h/mL to 310 ng.h/mL (S) - increase in t½ by 54%, from 1.9 h to 3.0 h (S) - difference in blood glucose response is non-significant. *1/*2 versus *1/*1: - no significant differences, except for the increase in t_{max} by 60%, from 1.25 h to 2.0 h (S)	Authors' conclusion: "Genetic polymorphisms of CYP2C9 markedly affect the pharmacokinetics of glimepiride. The influence of the CYP2C9*3 variant allele on glimepiride pharmacokinetics may be clinically significant." "Hence, to reduce the risk of hypoglycemia at the initiation of sulfonylurea therapy, the starting dose of glimepiride should probably be 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."

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.
- Cost-effectiveness analyses:
  - Fokoun C et al. Pharmacogenetic-guided glimepiride therapy in type-2 diabetes mellitus: a cost-effectiveness study. Pharmacogenomics J2021;21:559-65. PMID: 33731883.
    With genotype-guided therapy, the cost to avoid an episode of severe hypoglycaemia per 100,000 patients treated was calculated to be €421,834, which is not cost-effective. Genotyping cost was the most influential factor on the cost with the costs decreasing to € 96,139 for genotyping cost of €92.
    The authors conclude that the potential cost of CYP2C9 genotype-guided dosing for glimepiride therapy is relatively high, and associated with modest improvements with respect to the number of hypoglycaemia avoided, as compared with standard dosing.
    Genotype-guided therapy consisted of combined treatment with metformin and sitagliptin for *3/*3 and treatment with glimepiride for the other genotypes. Non-genotype-guided therapy consisted of glimepiride for all. For both genotype- and non-genotype-guided therapy, glimepiride was substituted for metformin and sitagliptin after an episode of severe hypoglycaemia. Patients were assumed to start on a glimepiride dose of 2 mg/day, which could be adjusted to 4 mg/day based on effectiveness.
    The calculation was performed for a treatment period of 1 year and from the perspective of the French national

health insurance system. Direct medical costs were calculated. Genotype-guided therapy of 100.000 patients was calculated to avoid 122 episodes of severe hypoglycaemias (3.2% of the number for non-genotype-guided therapy) against additional cost of €51 548 199 122. Calculations were based on a CYP2C9 *3/*3 prevalence of 0.006, a prevalence of severe hypoglycaemia in *3/*3 of 6.3% and a prevalence of severe hypoglycaemia in other genotypes of 3.7%, a percentage of severe hypoglycaemia under sulfonylureas requiring hospitalisation of 1.3%, cost of hospital care for severe hypoglycaemia of €5842, cost of glimepiride 2 mg of €0.145/tablet, cost of glimepiride 4 mg of €0.183/tablet, cost of metformine/sitagliptine combination of €0.53/tablet, and genotyping cost of €490.

Date of literature search: 24 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	4 AA[#]	Yes	No	
	*2/*2	4 AA	Yes	No	
	*2/*3	3 D	Yes	No	
	*3/*3	3 D	Yes	No	
	IM	--	Yes	No	
	PM	--	Yes	No	

[#] In the studies that found a significant clinical effect for *1/*3, this was a positive effect instead of a negative effect.

Mechanism:
Glimepiride is metabolised to weakly effective hydroxy glimepiride by CYP2C9. This metabolite is then converted by dehydrogenases to an inactive carboxy metabolite.