CYP2D6: doxepin 2596-2598

AUC = area under the concentration-time curve, Cl_{or} = oral clearance, C_{ss} = plasma concentration in steady state, CTCAE = common terminology criteria for adverse events, IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), MR = metabolic ratio, 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, TCA = tricyclic antidepressant, 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:
Doxepin and the active metabolite N-desmethyldoxepin (nordoxepin) are primarily converted by CYP2D6 to inactive hydroxy metabolites.
Genetic variants in CYP2D6 can result in a decreased CYP2D6 enzyme activity (intermediate metabolisers (IM)), an absent CYP2D6 enzyme activity (poor metabolisers (PM)) or an increased CYP2D6 enzyme activity (ultra-rapid metabolisers (UM)).
Kinetic studies showed (significant) differences in doxepin + nordoxepin exposure for patients with CYP2D6 gene variants (Kirchheiner 2005, Kirchheiner 2002 and Tacke 1992). Two cases suggest an increased risk for adverse events in PM (Koski 2007, Grasmader 2004). Because doxepin has a narrow therapeutic range, changes in exposure are likely to have therapeutic consequences. For these reasons, the KNMP Pharmacogenetics Working Group decided that a gene-drug interaction is present and that dose adjustments are required for PM, IM and UM (yes/yes-interactions).
Justification of choices per CYP2D6 phenotype
Dose adjustments have been calculated on the basis of the AUC or C_{ss} of doxepin + nordoxepin.
PM: A case of death by doxepin intoxication was reported for PM, in which the defective genotype probably contributed to the death. Dose adjustment or use is therefore desirable. The weighted mean of the calculated dose adjustment, based on a total of 12 PM from three studies (Kirchheiner 2005, Grasmader 2004, and Kirchheiner 2002), is a dose reduction to 44% of the normal dose (median 46%, 34-46% for the two studies, 114% for the case). This was rounded off to 40% to be more achievable in clinical practice.
IM: Only kinetic effects are known for IM, but - analogous to PM and based on the narrow therapeutic range of doxepin - dose adjustment is recommended. The calculated dose adjustment is a dose reduction to 84% of the normal dose (one study with 8 IM (Kirchheiner 2005)). This was rounded off to 80% to be more achievable in clinical practice.
UM: The calculated dose adjustment is a dose increase to 221% of the normal dose (one study with 6 UM (Kirchheiner 2002)). This was translated to 200% to be more achievable in clinical practice.
An alternative can be selected as a precaution due to the lack of knowledge about the effects of high concentrations of the possible cardiotoxic hydroxy metabolites.
Note: The reliability of the dose adjustment calculation is currently limited by the fact that it is not known which isomer is the active form, whilst Kirchheiner 2002 found that the metabolism of the E-isomer in particular is influenced by CYP2D6.
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 KNMP Pharmacogenetics Working Group considers genotyping before starting doxepin to be potentially beneficial for the prevention of side effects. 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 guide-

line.
The clinical implication of the gene-drug interaction scores 2 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):
A case of fatal doxepin intoxication was reported for PM, in which the defective genotype probably contributed to the death (severity score F, corresponding to CTCAE grade 5). This results in the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (2 points for CTCAE grade 5).
There were no studies showing an increase in adverse events in patients with CYP2D6 genetic variants. This results in a score of 0 of the maximum of 3 points for the second criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 (only points for at least one publication with level of evidence score ≥ 3).
A severe clinical effect has only been observed in a case report and not in studies, and only one case report with a severe clinical effect was found. This indicates that the number needed to genotype (NNG) to prevent one clinical effect code ≥ D (grade ≥ 3) cannot be determined, but is likely to be very high. This results in a score of 0 of the maximum of 3 points for the third criterion of the clinical implication score: the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3 (only points for NNG ≤ 1000).
The American Summary of Product Characteristics (SmPC) of doxepin mentions the CYP2D6 PM phenotype, but the Dutch SmPC (SmPC Sinequan (doxepine) 29-01-2015) does not. 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). Note: Doxepine is not registered in the Netherlands anymore since April 2023. Non-registered products are still available.

The table below follows the KNMP definitions for NM, PM, IM and UM. The definitions of NM, PM, IM and UM used in the table below may therefore differ from the definitions used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Koski A et al. A fatal doxepin poisoning associated with a defective CYP2D6 genotype. Am J Forensic Med Pathol 2007;28:259-61.	2 PM: F	Blood samples were collected following the death of a 43-year-old male. The plasma concentration of doxepin was 2.4 mg/L (therapeutic range approx. 0.03-0.15 mg/L) and that of nordoxepin was 2.9 ml/L. The cause of death was confirmed as fatal doxepin intoxication. MR doxepin/nordoxepin (0.83) was low in comparison to 20 other fatal doxepin intoxications (2.0-75, for 19 of the 20 intoxications it was 3.8-75). The man was found to be CYP2D6 *3/*4 and CYP2C19 *1/*1. As the low MR doxepin/nordoxepin did not correspond to acute intoxication, the authors consider it likely that the defective CYP2D6 genotype contributed to his death, probably as a result of repeated high doses of doxepin.	
ref. 2 Kirchheiner J et al. Impact of the CYP-2D6 ultra-rapid metabolizer genotype on doxepin pharmacokinetics and serotonin in platelets. Pharmacogenet Genomics 2005;15:579-87.	3 PM: A UM: A	A total of 25 healthy volunteers (11x NM (7x gene dose 2, 4x gene dose 1.5), 3x PM (gene dose 0), 6x UM (gene dose 3), 5x 'UM' (4x gene dose 2.5, 1x gene dose 2) received a single dose of doxepin 75 mg. PM versus NM: - increase in AUC doxepin + nordoxepin from 1061 to 2291 nmol.hour/L (S by 116%) UM versus NM: - decrease in AUC doxepin + nordoxepin from 1061 to 479 nmol.hour/L (S by 55%) 'UM' versus NM: - decrease in AUC doxepin + nordoxepin from 1061 to 562 nmol.hour/L (S by 47%) There was a significant negative correlation between the sum of the plasma concentrations of doxepin + nordoxepin and the systolic blood pressure, but no difference in heart rate, blood pressure, QTc or sedation between the various CYP2D6 genotypes.	AUC doxepin + nordoxepin versus NM: PM: 216% UM: 45% 'UM': 53%

ref. 2, continuation		NOTE: The results for 'UM' are described separately in this summary, because 20% of these cases involved the genotype n x 0.5 – 1 (gene dose 2). According to the KNMP definition, gene dose 2 is an NM. NOTE: Genotyping was performed for the alleles *3, *4, *5, *6, *9, *10, *35, *41 and for gene duplication of *1, *2, *4, *9, *10 and *41.	
ref. 3 Grasmader K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.	3 (1) PM: C	Genotyping was performed on 4 patients on doxepin (dose unknown). Out of the 4 patients, one was CYP2D6 PM and the other three were either CYP2D6 IM or NM. Relevant co-medication was not excluded. The mean dose-corrected C_{ss} of doxepin + nordoxepin was 0.27 ng/mL per mg of dosed doxepin. For the PM, the corrected plasma concentration was 12% lower than the mean. The PM had relevant side effects.	Plasma concentration doxepin + nordoxepin versus NM (+ IM): PM: 88%
ref. 4 Kirchheiner J et al. Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. Pharmacogenetics 2002;12:571-80.	3 PM: A IM: A	A total of 42 healthy volunteers (8x *1/*1, 7x *1/*4, 1x *1/*5, 6x *4/*4, 1x *4/*5, 1x *3/*5; all CYP2C19 NM and CYP2C9 NM) received a single dose of doxepin 75 mg. PM versus NM: - increase in AUC doxepin + $AUC_{0\text{-}48h}$ nordoxepin from 1.43 to 4.15 µmol.hour/L (S by 190%) - decrease in Cl_{or} doxepin from 6.2 to 1.4 L/hour per kg (S by 77%) - increase in relative biological availability of E-doxepin from 0.56 to 1.00 (S not calculated; by 79%) IM versus NM: - increase in AUC doxepin + $AUC_{0\text{-}48h}$ nordoxepin from 1.43 to 1.70 µmol.hour/L (S by 19%) - decrease in Cl_{or} doxepin from 6.2 to 3.6 L/hour per kg (S by 42%) - increase in relative biological availability of E-doxepin from 0.56 to 0.72 (S not calculated; by 29%) The difference in clearance is primarily caused by a difference in clearance of the E-isomer of doxepin. The increased biological availability is probably caused by a decreased first pass effect. NOTE: Genotyping was performed for the alleles *3, *4, *5 and *6 and for gene duplication.	Authors' conclusion: "The CYP2D6 polymorphism had a major impact on E-doxepin pharmacokinetics and CYP-2D6 PMs might be at an elevated risk for adverse drug effects when treated with common recommended doses." AUC doxepin + nordoxepin versus NM: PM: 290% IM: 119%
ref. 5 Tacke U et al. Debrisoquine hydroxylation phenotypes of patients with high versus low to normal serum antidepressant concentrations. J Clin Psychopharmacol 1992;12:262-7.	3 PM: AA	4 cases with high plasma concentrations at normal doses of doxepin were compared to 4 carefully selected controls with low to normal plasma concentrations. Phenotyping revealed that 50% of the cases and 0% of the controls were PM for CYP2D6 (S not determined). Differences in medication at the time of phenotyping were not ruled out. NOTE: genotype unknown	
ref. 6 SmPC Silenor (doxepin) 29-10-20, USA.	0	<u>Clinical pharmacology</u>: Poor Metabolizers of CYPs Poor metabolizers of CYP2C19 and CYP2D6 may have	

ref. 6, continuation	PM: AA	higher doxepin plasma levels than normal subjects.	

Risk group	IM with CYP2D6 inhibitor

Comments:

- The case report of Whitledge 2023 was not included in this risk analysis, because the administered dose was 1.5 times the maximum off label dose in children (Whitledge JD et al. Chronic doxepin toxicity masquerading as epilepsy in a 10-year-old boy. J Med Toxicol 2023;19:405-10. PMID: 37682427). It is not known whether chronic toxicity would have occurred in this IM patient when this maximum dose would not have been exceeded.
  The case report of Russell 2023 was not included in this risk analysis, because the patient used the strong CYP2D6 inhibitor fluoxetine concomitantly (Russell J et al. Case report: performing a medication safety review assisted by pharmacogenomics to explain a prescribing cascade resulting in a patient fall. Medicina (Kaunas) 2023; 59:118. PMID: 36676742). Because strong CYP2D6 inhibitors are known to be able to convert both NM and IM to phenotypically PM, it is not known whether doxepin would have contributed less to the excessive sedation if the patient would have been NM instead of IM.
- Existing guideline:
  Hicks JK et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017;102:37-44, PubMed PMID: 27997040 and October 2019 update on the CPIC site (modifications to CPIC's prior system of genotype-phenotype translation, including downgrading the value assigned to the CYP2D6*10 allele for activity score calculation from 0.5 to 0.25 and changing the phenotype assignment for an activity score of 1 from normal metaboliser to intermediate metaboliser).
  CPIC uses the same definition for NM, IM and PM as we do. However, CPIC uses a different definition for UM (gene dose ≥ 2.5 instead of ≥ 2.75), because CPIC did not decide to include gene dose 2.5 in NM until most laboratories can determine which allele has been duplicated and therefore can distinguish between e.g. *1x2/*41 (gene dose 2.5) and *1/*41x2 (gene dose 2). The summary below uses the KNMP definitions for NM, PM, IM and UM.
  CPIC uses amitriptyline as a representative TCA for this guideline. CPIC states that the results of the amitriptyline studies may apply to other TCAs because these drugs have comparable pharmacokinetic properties (the reviews Rudorfer MV et al. Metabolism of tricyclic antidepressants. Cell Mol Neurobiol 1999;19:373-409 and Stingl JC et al. Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. Mol Psychiatry 2013;18:273-87). In addition, extrapolated dose adjustments based on metaboliser status are similar across the tricyclic class (Stingl 2013). CPIC also uses amitriptyline as a representative for doxepin, although literature suggests a higher first pass metabolism of doxepin compared to the other TCAs (approximately 70% for doxepin compared to an average value of approximately 50%) (Rudorfer 1999).
  CPIC uses amitriptyline as a representative TCA for this guideline. CPIC states that the results of the amitriptyline studies may apply to other TCAs because these drugs have comparable pharmacokinetic properties (the reviews Rudorfer MV et al. Metabolism of tricyclic antidepressants. Cell Mol Neurobiol 1999;19:373-409 and Stingl JC et al. Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. Mol Psychiatry 2013;18:273-87). In addition, extrapolated dose adjustments based on metaboliser status are similar across the tricyclic class (Stingl 2013).
  For amitriptyline, CPIC states that the recommended starting dose of amitriptyline does not need dose adjustment for NM. In addition, CPIC states that a 25% reduction of the recommended dose may be considered for patients with a CYP2D6 gene dose of 0.5. As a reference for this percentage reduction they mention the 2011 publication of our dosing recommendations in Clinical Pharmacology and Therapeutics. However, this dosing recommendation is primarily based on patients with gene dose 1. In addition, we changed the percentage reduction in 2011 from 25% to 40%, based on the switch from using the sum of the plasma concentrations of amitriptyline and nortriptyline to using the plasma concentration of nortriptyline for dose calculations. Because patients with a CYP2D6 activity score of 1.0 are inconsistently categorised as intermediate or normal metabolisers in the literature, making these studies difficult to evaluate, CPIC classified the strength of the recommendation for gene dose 0.5 as moderate (i.e. there is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects). After the October 2019 update, CPIC states that a 25% reduction of the recommended dose may also be considered for patients with a CYP2D6 gene dose of 1.
  CPIC states that CYP2D6 ultra-rapid metabolisers + gene dose 2.5 have a higher probability of failing amitriptyline pharmacotherapy due to subtherapeutic plasma concentrations, and alternate agents are preferred.
  CPIC states that, if amitriptyline is warranted, there are insufficient data in the literature to calculate a starting dose for a patient with CYP2D6 ultra-rapid metaboliser or gene dose 2.5 status, and therapeutic drug monitoring is strongly recommended.

Based on a nortriptyline study, CPIC indicates that adverse effects are more likely in CYP2D6 poor metabolisers due to elevated tricyclic plasma concentrations; therefore, alternate agents are preferred. If a tricyclic is warranted, CPIC recommends to consider a 50% reduction of the usual dose, and strongly recommends therapeutic drug monitoring.
Because the TCAs have comparable pharmacokinetic properties, CPIC states that it may be reasonable to extrapolate the amitriptyline guideline to other TCAs, including doxepin, with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline.
Thus, the therapeutic recommendations for doxepin are identical to the therapeutic recommendations for amitriptyline with only the classification of the recommendations adapted to the fewer supporting clinical and pharmacokinetic data:

Dosing recommendations for doxepin for conditions requiring higher doses such as depression based on CYP2C19 phenotype[a,b]		
Phenotype	Therapeutic recommendation	Classification of recommendation
UM + gene dose 2.5	Avoid doxepin use due to potential lack of efficacy. Consider alternative drug not metabolised by CYP2D6. If doxepin is warranted, consider titrating to a higher target dose (compared to normal metabolisers).[c] Utilise therapeutic drug monitoring to guide dose adjustments.	Strong[e]
NM	Initiate therapy with recommended starting dose.[d]	Strong[e]
gene dose 1	Consider a 25% reduction of recommended starting dose.[d] Utilise therapeutic drug monitoring to guide dose adjustments.[c]	Optional[f]
gene dose 0.5	Consider a 25% reduction of recommended starting dose.[d] Utilise therapeutic drug monitoring to guide dose adjustments.[c]	Moderate[g]
PM	Avoid doxepin use due to potential for side effects. Consider alternative drug not metabolised by CYP2D6. If doxepin is warranted, consider a 50% reduction of recommended starting dose.[d] Utilise therapeutic drug monitoring to guide dose adjustments.[c]	Strong[e]

[a] Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. For conditions at which lower initial doses are used, such as neuropathic pain, CPIC recommends no dose modifications for PM or gene dose 0.5, because it is less likely that PM or gene dose 0.5 will experience adverse effects due to supra-therapeutic plasma concentrations of the TCA. However, CPIC indicates that these patients should be monitored closely for side effects. In addition, if larger doses of TCA are warranted, CPIC recommends following the gene-based dosing guidelines in the table above. For UM+gene dose 2.5, CPIC recommends considering an alternative agent. Based on predicted and observed pharmacokinetic data in those with depression, CYP2D6 UM+gene dose 2.5 may be at an increased risk of failing TCA therapy for neuropathic pain due to lower than expected drug concentrations (Dworkin RH et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;13: 237-51).

[b] Because the tricyclics have comparable pharmacokinetic properties, it may be reasonable to apply these amitriptyline recommendations to other tricyclics, including doxepin, with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline.

[c] Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.

[d] Patients may receive an initial low dose of doxepin, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

[e] Strong indicates that "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."

[f] Optional indicates that the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

[g] Moderate indicates that "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

As evidence linking CYP2D6 genotype with doxepin phenotype, CPIC mentions Neukamm 2013, Bijl 2008, Koski 2007, Kirchheiner 2005, Kirchheiner 2002, Haritos 2000 and Tacke 1992. These studies, except for Neukamm 2013, Bijl 2008, and Haritos 2000 are included in our risk analysis. Neukamm 2013 was not included in our risk analysis because it is a post-mortem analysis of a fatal doxepin poisoning case with the NM phenotype (gene dose 1.5) using 18 other medications including one that is probably a strong CYP2D6 inhibitor. Bijl 2008 was not included because only 4 of the 1198 patients in the study (among whom 807 TCA users) used doxepin, and genotypes and results were not reported separately for doxepin. Haritos 2000 was not included because it was an *in vitro* study. In addition to the studies considered by CPIC, our risk analysis includes the small study of Grasmader 2004. CPIC indicates that the studies provide a high level of evidence for a decreased doxepin metabolism in PM and for an increased doxepin metabolism in UM+gene dose 2.5 compared to gene dose 1-2 (based on 4 references including Haritos 2000 for PM and on 1 reference for UM+gene dose 2.5). In addition, CPIC indicates that these studies provide a high level of evidence for a correlation between the number/function of CYP2D6 variant alleles and metabolism of doxepin (2 references). Contrary to this, CPIC indicates a weak level of evidence for the requirement of a lower dose of doxepin by PM as compared to gene dose 1-2 (Bijl 2008). In addition, CPIC indicates that these studies provide a moderate level of evidence for an increased risk for side effects in carriers of no function alleles or decreased func-

tion alleles compared to carriers of other alleles (3 studies including Neukamm 2013 and Bijl 2008).
CPIC also provides therapeutic recommendations based on both CYP2D6 and CYP2C19 genotypes. For CYP2D6 UM+gene dose 2.5 and for CYP2D6 PM the therapeutic recommendations for the different CYP-2C19 phenotypes are similar, reflecting the stronger influence of the CYP2D6 phenotype compared to the CYP2C19 phenotype. CPIC indicates that further studies are needed to develop moderate or strong dosing recommendations for TCAs when considering combined CYP2D6/CYP2C19 phenotypes. At the moment, insufficient data are available. Based on Steimer 2005, CPIC mentions that patients carrying at least one CYP2D6 no function allele and two CYP2C19 normal function alleles had an increased risk of experiencing side effects when administered amitriptyline. This would argue for a therapeutic recommendation also for patients with CYP2D6 gene dose 1, which is the predominant phenotype in this patient group.
On 11-12-2023, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of literature search:11 December 2023.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	3F	Yes	Yes	8 February 2024
	IM	3A	Yes	Yes	
	UM	3A	Yes	Yes	

Mechanism:
Doxepin and the active metabolite N-desmethyldoxepin (nordoxepin) are primarily converted by CYP2D6 to inactive hydroxy metabolites. Doxepin is mainly converted by CYP2C19 to nordoxepin. The therapeutic range is 100-250 ng/ml for the sum of doxepin and nordoxepin and values higher than 400 ng/ml are considered to be toxic. The therapeutic range of doxepin is considered to be 50-150 ng/ml and of nordoxepin 50-100 ng/ml.
The Z-hydroxymetabolites of amitriptyline and nortriptyline are known to be cardiotoxic. It cannot be excluded that the Z-hydroxymetabolites of doxepin and nordoxepin are also cardiotoxic.

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+	2+
Corresponding Clinical Implication Score:		Potentially beneficial