48% of the HLA-B*5701-positive patients develop a severe and potentially life-threatening hypersensitivity reaction to abacavir. Abacavir is contra-indicated for HLA-B*5701-positive patients.

- avoid abacavir

Literature:

CYP2C9 IM ANDERS: acenocoumarol
NO action is needed for this gene-drug interaction.
CYP2C9 PM ANDERS: acenocoumarol

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

**Literature:**


Date 14-05-2018

CYP2C9*1/*2: acenocoumarol

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

**Literature:**


Date 14-05-2018
Literature:


Date 14-05-2018

CYP2C9*1/*3: acenocoumarol

1864

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

Literature:

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as no action is needed for this gene-drug interaction.

Date 14-05-2018

CYP2C9*2/*3: acenocoumarol

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as no action is needed for this gene-drug interaction.

Literature:

Date 14-05-2018

CYP2C9*3: acenocoumarol

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).
CYP2C9*3/*3: acenocoumarol

NO action is needed for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose and possibly an increase in the time needed to reach a stable INR. However, there is insufficient evidence that this causes problems when therapy is initiated as usual (i.e. with frequent INR monitoring).

Literature:

VKORC1 -1639 AA: acenocoumarol

An INR ≥ 6, resulting in an increased risk of bleeding, occurs in 8-12% of these patients during the first weeks of treatment with standard regulation by the Anticoagulation Clinic. The genetic variation increases the sensitivity to acenocoumarol.

- Monitoring by the ANTICOAGULATION CLINIC (National INR Monitoring Service):
  - recommend to use 50% of the standard initial dose
- OTHERWISE:
  - recommend to use 50% of the standard initial dose
  - recommend more frequent monitoring of the INR

The initial dose and the maintenance dose can be calculated using an algorithm. However, for patients with two or more VKORC1 and/or CYP2C9 variations, the algorithm used in EU-PACT (see https://www.knpmp.nl/patientenzorg/medicatiebewaking/farmacogenetica for a calculation tool in the form of an Excel file) did not result in a significant reduction in the incidence of INRs above the target range when compared to an algorithm without genetic information. We are therefore unable to recommend the use of this algorithm at this time.

A (non-validated) algorithm has been prescribed for children that should result in a better prediction of the maintenance dose for AA than the current guideline used by the Anticoagulation Clinic.


Literature:
VKORC1 -1639 GA: acenocoumarol

NO action is needed for this gene-drug interaction.

The genetic variation results in a reduction of the required dose, but with the current practice of initiating or reviewing treatment this results in little or no increased risk of bleeding or excessive anticoagulation.

Literature:

ABC2G 141KK: allopurinol

The effectiveness of allopurinol is reduced, meaning that a higher dose is required. The gene variation reduces the excretion of uric acid by kidneys and intestines, meaning that a stronger inhibition of the uric acid production by allopurinol is required to achieve the desired uric acid concentration.

- use 1.4 times the standard dose
This equates to a dose titration schedule of 100, 300, 400, 600 and 700 mg/day instead of the usual schedule of 100, 200, 300, 400 and 500 mg/day.

Literature:

ABC2G 141QK: allopurinol

The effectiveness of allopurinol is reduced, meaning that a higher dose is required. The gene variation reduces the excretion of uric acid by kidneys and intestines, meaning that a stronger inhibition of the uric acid production by allopurinol is required to achieve the desired uric acid concentration.

- use 1.25 times the standard dose
This equates to a dose titration schedule of 100, 200, 400 and 500 mg/day instead of the usual schedule of 100, 200, 300 and 400 mg/day.

Literature:

Date 07-06-2021

**HLA-B*5801: allopurinol**

A strongly increased risk of developing the life-threatening cutaneous side effects Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and DRESS is present in patients with this genetic variation. The risk of an allopurinol-induced life-threatening cutaneous side effect (mortality 11%) in these patients is 1.6-2.0% for the entire group and 8-18% for the group with chronic renal insufficiency.

- Choose an alternative, such as febuxostat

Another option is to induce allopurinol tolerance first:

To induce allopurinol tolerance, the allopurinol dose is increased every 3 days until a dose of 100 mg/day has been achieved on Day 28. The consecutive daily doses in the induction protocol are 50 µg, 100 µg, 200 µg, 500 µg, 1 mg, 5 mg, 10 mg, 25 mg, 50 mg and 100 mg.

**Literature:**

13. SPC Zyloric.

**Date 07-06-2021**

**CYP2D6 IM: amiodaron**

This is NOT a gene-drug interaction.

**Literature:**

- Date 24-08-2016

**CYP2D6 PM: amiodaron**

This is NOT a gene-drug interaction.

**Literature:**

- Date 24-08-2016

**CYP2D6 UM: amiodaron**

This is NOT a gene-drug interaction.

**Literature:**

- Date 24-08-2016

**CYP2C19 IM: amitriptyline**

NO action is required for this gene-drug interaction.

The gene variation has an effect on the exposure to amitriptyline, but not on the exposure to amitriptyline + the active metabolite nortriptyline, which determines the effect and side effects.
Literature:

Date 04-03-2019

CYP2C19 PM: amitriptyline

NO action is required for this gene-drug interaction.

The gene variation has an effect on the exposure to amitriptyline, but not on the exposure to amitriptyline + the active metabolite nortriptyline, which determines the effect and side effects.

Literature:
8. SmPC Amitriptyline HCl Apotex.

Date 04-03-2019

CYP2C19 UM: amitriptyline

NO action is required for this gene-drug interaction.

The gene variation decreases the exposure to amitriptyline and increases the exposure to the active metabolite nortriptyline, but there is no evidence to indicate that this results in an increase in side effects or a decrease in efficacy. A higher dose is required to achieve the therapeutic range of amitriptyline+nortriptyline, but the therapeutic range of nortriptyline is achieved at the lower dose.

Literature:

Date 04-03-2019

CYP2D6 IM: amitriptyline

The risk of side effects is increased, because the gene variation leads to higher plasma concentrations of the active metabolite nortriptyline and to a lesser extent of amitriptyline.

Recommendation:
- use 75% of the standard dose and monitor the efficacy and side effects or the plasma concentrations of amitriptyline and nortriptyline to adjust the maintenance dose.

Literature:
CYP2D6 PM: amitriptyline

In theory, risk of side effects is increased, because the genetic variation results in higher plasma concentrations of the active metabolite nortriptyline and to a lesser extent of amitriptyline.

- use 70% of the standard dose and monitor the effect and side effects or the plasma concentrations of amitriptyline and nortriptyline to adjust the maintenance dose

CYP2D6 UM: amitriptyline

The risk of ineffectiveness is increased and the risk of cardiotoxic side effects may be increased. The gene variation leads to increased conversion of amitriptyline and the active metabolite nortriptyline to less active and inactive metabolites.

- increase the dose to 1.4 times the standard dose, monitor the effect and side effects or the plasma concentrations and be alert to increased plasma concentrations of the cardiotoxic Z-10-hydroxy metabolites.

- Plasma concentrations of Z-hydroxy nortriptyline or Z-hydroxy amitriptyline higher than 40 ng/mL are considered toxic.

- if a dose increase is not desirable due to the cardiotoxic hydroxy metabolite: avoid amitriptyline Anti-depressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Literature:


The heterozygously present genetic polymorphism “factor V Leiden” causes an increased tendency to coagulation, resulting in an increased risk of venous thromboembolism. Contraceptives containing oestrogens can increase this risk even further.

Recommendation:

- If the patient has a FAMILY HISTORY WITH A LOT OF THROMBOSIS, or has had a PREVIOUS THROMBOSIS:
  1. Advise the prescriber to avoid the use of contraceptives that contain oestrogens and prescribe a non-hormone contraceptive - such as a copper IUD - as an alternative. One could also opt for a progesteron-only contraceptive method, such as the depot injection, an IUD with levonorgestrel or an implant with etonogestrel.
- OTHER CASES:
  1. Advise the patient to avoid additional risk factors for thrombosis (obesity, smoking, etc.).

Literature:

The risk of side effects is increased. The genetic variation leads to an increase in the sum of the plasma concentrations of aripiprazole and the active metabolite.

- administer no more than 10 mg/day or 300 mg/month (68-75% of the standard maximum dose of aripiprazole).
This is NOT a gene-drug interaction.
The risk of myopathy may be increased. The gene variation may lead to reduced atorvastatin transport to the liver, which may increase the atorvastatin plasma concentration.

**Recommendation:**
- Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy:
  1. Choose an alternative
     Do not select simvastatin, as this is also affected by the SLC01B1 gene variation. Rosuvastatin and pravastatin are influenced to a similar extent by SLC01B1 polymorphisms, but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not influenced significantly by SLC01B1 gene variation or CYP3A4 inhibitors.
  2. If an alternative is not an option: advise the patient to contact their doctor in the event of muscle symptoms.
- Patient has NO additional significant risk factors for statin-induced myopathy:
  1. Advise the patient to contact their doctor in the event of muscle symptoms.


7. de Keizer CE et al. The SLCO1B1 c.521T>G polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. Pharmacogenet Genomics 2014;24:43-51.


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SLCO1B1 521TC: atorvastatin

The risk of myopathy can be evaluated. The gene variation may lead to reduced atorvastatin transport to the liver, which may increase atorvastatin plasma concentrations.

- **Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy:**
  1. Choose an alternative.
  2. Rosuvastatin and pravastatin are influenced to a similar extent by the SLCO1B1 gene variation, but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.
  3. Rosuvastatin and pravastatin are not influenced significantly by the SLCO1B1 gene variation or CYP3A4 inhibitors.

- **If an alternative is not an option: advise the patient to contact their doctor in the event of muscle symptoms.**
  1. Advise the patient to contact their doctor in the event of muscle symptoms.

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Literature:


7. de Keizer CE et al. The SLCO1B1 c.521T>G polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. Pharmacogenet Genomics 2014;24:43-51.


Note: The percentage of 50% is based on the analogy with TPMT, for which the gene variants have a comparable effect on toxicity to those of NUDT15. A percentage of < 70% was calculated for NUDT15, but there were insufficient data available to calculate the exact percentage.

Note: Dose adjustment based on the total of 6-TGN metabolites is not possible for these patients, as they develop toxicity within the therapeutic range that applies for patients without gene variants.

- **LEUKAEMIA:**
  - start at 50% of the standard mercaptopurine dose, or start with the standard dose and reduce to 50% if side effects necessitate a dose reduction
  - Adjustment of the initial dose should be performed based on toxicity (monitoring of the blood counts) and efficacy.

Note: The percentage of 50% is based on the analogy with TPMT, for which the gene variants have a comparable effect on toxicity to those of NUDT15. A percentage of < 70% was calculated for NUDT15, but there were insufficient data available to calculate the exact percentage.

Note: Dose adjustment based on the total of 6-TGN metabolites is not possible for these patients, as they develop toxicity within the therapeutic range that applies for patients without gene variants.

Note: more stringent dose reductions are necessary if the patient is also TPMT IM or TPMT PM.

**LEUKAEMIA:**

**Dose adjustment** based on the total of 6-TGN metabolites is not possible for these patients, as they develop toxicity within the therapeutic range that applies for patients without gene variants.

**Note:** more stringent dose reductions are necessary if the patient is also TPMT IM or TPMT PM.

**LEUKAEMIA:**
- start at 50% of the standard mercaptopurine dose, or start with the standard dose and reduce to 50% if side effects necessitate a dose reduction
  - Adjustment of the initial dose should be performed based on toxicity (monitoring of the blood counts) and efficacy.

**Note:** The percentage of 50% is based on the analogy with TPMT, for which the gene variants have a comparable effect on toxicity to those of NUDT15. A percentage of < 70% was calculated for NUDT15, but there were insufficient data available to calculate the exact percentage.

**Note:** Dose adjustment based on the total of 6-TGN metabolites is not possible for these patients, as they develop toxicity within the therapeutic range that applies for patients without gene variants.

**Note:** more stringent dose reductions are necessary if the patient is also TPMT IM or TPMT PM.
It is not known whether dose reduction in advance results in the same efficacy as dose reduction based on toxicity. The initial dose should be adjusted based on toxicity (monitoring of the blood counts) and efficacy.

Note: more stringent dose reductions are necessary if the patient is also NUDT15 IM or NUDT15 PM.

Literature:

8. Kim MJ et al. Monitoring 2015.37.1. more stringent dose reductions are necessary if the patient is also NUDT15 IM or NUDT15 PM.
There are indications supporting an increase in the exposure to brexpiprazole, but no indications supporting an increase in side effects in patients with this gene variation. NO action is required for this gene-drug interaction.

Date 08-02-2021

CYP2D6 IM: bisoprolol

This is NOT a gene-drug interaction.

Literature:

Date 08-02-2021

CYP2D6 PM: bisoprolol

This is NOT a gene-drug interaction.

Literature:
1. Deroubaix X et al. Comparative bioavailability of a metoprolol controlled release formulation and a bisoprolol normal release tablet after single oral dose administration in healthy volunteers.

Date 08-02-2021

CYP2D6 UM: bisoprolol

This is NOT a gene-drug interaction.

Literature:

Date 08-02-2021

CYP2D6 IM: brexpiprazol

NO action is required for this gene-drug interaction.

There are indications supporting an increase in the exposure to brexpiprazole, but no indications supporting an increase in side effects in patients with this gene variation.

Literature:
2. EPAR Rexulti.
CYP2D6: brexpiprazol

The risk of side effects is theoretically increased, because the gene variation reduces the metabolism of brexpiprazole.

- use half of the standard dose

Literature:
1. SmPC en EPAR Rexulti (NL) en SmPC Rexulti (VS).

CYP2D6: brexpiprazol

NO action is required for this gene-drug interaction.

The gene variation results in a reduction of the exposure to brexpiprazole, but there are no indications supporting a decrease in efficacy.

Literature:
1. EPAR Rexulti.

HLA-A*3101: carbamazepine

Patients with this genetic variation have an increased risk of experiencing the life-threatening cutaneous adverse events DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The risk of carbamazepine-induced DRESS in these patients is 0.89%.

Recommendation:
1. carefully weigh the risk of DRESS and SJS/TEN against the benefits
2. if an alternative is an option, choose an alternative

Literature:
5. SPC’s Tegretol (NL en VS).

HLA-B*1502: carbamazepine

Patients with this genetic variation have a severely increased risk of experiencing the life-threatening cutaneous adverse event Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The risk of carbamazepine-induced SJS/TEN in these patients is 1.8-3.4%.

Recommendation:
1. choose an alternative if possible
   Phenytion, lamotrigine and oxcarbazepine also pose an increased risk of SJS/TEN in these patients, but the final risk is 10-fold lower for these medicines than for carbamazepine.
   Furthermore, in the case of oxcarbazepine, the most severe forms (SJS/TEN overlap and TEN) have not been observed.

Literature:
6. SPC’s Tegretol (NL en VS).

HLA-B*1511: carbamazepine

Patients with this genetic variation have an increased risk of experiencing the life-threatening cutaneous adverse event Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The risk of carbamazepine-induced SJS/TEN in patients with the HLA-B*1502 allele, which carries a 4.6-6.6 times higher risk than the HLA-B*1511 allele, is 1.8-3.4%. This would equate to a risk of carbamazepine-induced SJS/TEN in these patients of 0.27-0.73%.

Recommendation:
1. carefully weigh the risk of SJS/TEN against the benefits
the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset.

The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset.

- Do not exceed the following daily doses:
  1. adults up to 65 years: 30 mg as tablets or 22 mg as drops
  2. adults 65 years or older: 15 mg as tablets or 10 mg as drops

Literature:

Date 31-10-2016

CYP2D6 IM: carvedilol

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be elevated. This does not, however, result in an increase in side effects.

Date 24-08-2016

CYP2D6 PM: carvedilol

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be elevated. This does not, however, result in an increase in side effects.

Date 24-08-2016

CYP2D6 UM: carvedilol

NO action is required for this gene-drug interaction.

The plasma concentration of carvedilol can be reduced. This does not, however, result in a decrease in the effectiveness.

Date 24-08-2016

CYP2C19 IM: citalopram

The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset.

- Do not exceed the following daily doses:
  1. adults up to 65 years: 30 mg as tablets or 22 mg as drops
  2. adults 65 years or older: 15 mg as tablets or 10 mg as drops

Literature:

Date 24-08-2016

CYP2C19 UM: citalopram

The plasma concentration of citalopram can be reduced. This does not, however, result in a decrease in the effect. NO action is required for this gene-drug interaction.

The plasma concentration of citalopram can be elevated. This does not, however, result in an increase in side effects.

Date 24-08-2016

CYP2C19 PM: citalopram

NO action is required for this gene-drug interaction.

The plasma concentration of citalopram can be increased. This does not, however, result in an increase in side effects.

Date 24-08-2016

CYP2C19 UM: citalopram

The plasma concentration of citalopram can be increased. This does not, however, result in an increase in side effects.

Date 24-08-2016

CYP2C19 PM: citalopram

NO action is required for this gene-drug interaction.

The plasma concentration of citalopram can be increased. This does not, however, result in an increase in side effects.

Date 24-08-2016

CYP2C19 UM: citalopram

The plasma concentration of citalopram can be increased. This does not, however, result in an increase in side effects.

Date 24-08-2016

CYP2C19 PM: citalopram

NO action is required for this gene-drug interaction.

The plasma concentration of citalopram can be increased. This does not, however, result in an increase in side effects.

Date 24-08-2016

CYP2C19 UM: citalopram

The plasma concentration of citalopram can be increased. This does not, however, result in an increase in side effects.

Date 24-08-2016

CYP2C19 PM: citalopram

NO action is required for this gene-drug interaction.

The plasma concentration of citalopram can be increased. This does not, however, result in an increase in side effects.
CYP2C19 PM: citalopram

The risk of QT prolongation and therefore also the theoretical risk of torsades de pointes is increased as the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the increased risk of QT prolongation will be offset.

- do not exceed the following daily doses (50% of the standard maximum dose):
  1. adults up to 65 years: 20 mg as tablets or 16 mg as drops
  2. adults 65 years or older: 10 mg as tablets or 8 mg as drops

Literature:


Date 14-05-2018

CYP2C19 UM: citalopram

NO action is needed for this gene-drug interaction.

The gene variation increases conversion of citalopram to a weakly active metabolite. However, there is no significant effect on the plasma concentration of citalopram, the tolerance or the response.

Literature:


Date 14-05-2018

CYP2D6 IM: citalopram/escitalopram

This is NOT a gene-drug interaction.

Literature:

10. SPC Cipramil en Celexa (VS).
CYP2D6 PM: citalopram/escitalopram

This is NOT a gene-drug interaction.

Literature:
9. SPC’s Cipramil, Lexapro (NL en VS) en Celexa (VS).

CYP2D6 UM: citalopram/escitalopram

This is NOT a gene-drug interaction.

Literature:
5. SPC Cipramil.

CYP2C19 IM: clomipramine

NO action is required for this gene-drug interaction.

The gene variation increases clomipramine plasma concentrations, but not clomipramine+desmethylclomipramine plasma concentrations, which determines side effects and efficacy in depression. The increase in the plasma concentration of clomipramine is favourable for the efficacy in anxiety and obsessive compulsive disorder.

Literature:

CYP2C19 PM: clomipramine

NO action is required for this gene-drug interaction.

The gene variation increases the plasma concentration of clomipramine. However, there is insufficient evidence to substantiate an increase of the plasma concentration of clomipramine+desmethylclomipramine to such an extent that it increases the risk of side effects. The increase in the plasma concentration of clomipramine is favourable for the efficacy in anxiety and obsessive compulsive disorder.

Literature:

CYP2C19 UM: clomipramine

The gene variation increases the risk of ineffectiveness for obsessive compulsive disorder and anxiety disorders by reducing the plasma concentration of clomipramine. The gene variation has little to no effect on the plasma concentration of clomipramine+desmethylclomipramine, which determines the efficacy for depression and side effects.

- Indication OBSESSIVE COMPULSIVE DISORDER or ANXIETY DISORDERS:
  - avoid clomipramine
  Antidepressants that are not metabolised by CYP2C19 - or to a lesser extent - include, for example, fluoxetine, fluvoxamine and paroxetine.
The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of clomipramine and the active metabolite desmethylclomipramine.

- Indication DEPRESSION:
  - no action required

Literature:


Date 19-11-2018

CYP2D6 IM: clomipramine

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of clomipramine and the active metabolite desmethylclomipramine.

- use 70% of the standard dose and monitor the effect and side effects or the plasma concentrations of clomipramine and desmethylclomipramine

For depression, the therapeutic range is 200-400 ng/mL for the sum of the plasma concentrations of clomipramine and desmethylclomipramine.

For anxiety disorders, the therapeutic plasma concentration of clomipramine is approximately 100 ng/mL, in combination with a plasma concentration of desmethylclomipramine lower than 200 ng/mL. For obsessive compulsive disorder, the therapeutic plasma concentration of clomipramine is higher than 200 ng/mL, in combination with a plasma concentration of desmethylclomipramine that is as low as possible.

A sum of the plasma concentrations of clomipramine and desmethylclomipramine higher than 600 ng/mL is considered toxic.

Literature:

A sum of the plasma concentrations of clomipramine and desmethyloclopramine higher than 600 ng/mL is considered toxic, whilst the therapeutic upper limit for depression is 400 ng/mL.

- if dose reduction does not have the desired effect: avoid clomipramine

Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Literature:
11. SmPC Anafranil (VS).

Date 19-11-2018

**CYP2D6 UM: clomipramine**

The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of clomipramine and the active metabolite desmethyloclopramine and to increased concentrations of the potentially cardiotoxic hydroxy metabolites.

- use 1.5 times the standard dose and monitor the effect and side effects of the plasma concentrations of clomipramine and desmethyloclopramine to set the maintenance dose.

For depression, the therapeutic range is 200-400 ng/mL for the sum of the plasma concentrations of clomipramine and desmethyloclopramine.

For anxiety disorders, the therapeutic plasma concentration of clomipramine is approximately 100 ng/mL, in combination with a plasma concentration of desmethyloclopramine lower than 200 ng/mL.

For obsessive compulsive disorder, the therapeutic plasma concentration of clomipramine is higher than 200 ng/mL, in combination with a plasma concentration of desmethyloclopramine that is as low as possible.

- if a dose increase is not wanted due to potential cardiotoxic hydroxy metabolites: avoid clomipramine.

Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Literature:

Date 19-11-2018

**CYP2D6 IM: clonidine**

This is NOT a gene-drug interaction.

Literature:

Date 24-08-2016

**CYP2D6 PM: clonidine**

This is NOT a gene-drug interaction.

Literature:

Date 24-08-2016

**CYP2D6 UM: clonidine**

This is NOT a gene-drug interaction.
CYP2C19 IM: clopidogrel

The risk of serious cardiovascular and cerebrovascular events is increased in patients undergoing balloon angioplasty or stent placement (percutaneous coronary intervention) and in patients with a stroke or TIA, as the genetic variation reduces the activation of clopidogrel. No negative clinical consequences have been observed in other patients.

- PERCUTANEOUS CORONARY INTERVENTION, STROKE or TIA:
  - choose an alternative or double the dose to 150 mg/day (600 mg loading dose)

- Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent).

- OTHER INDICATIONS:
  - no action required

Literature:


Date 23-12-2019
The risk of serious cardiovascular and cerebrovascular events is increased in patients undergoing balloon angioplasty or stent placement (percutaneous coronary intervention) and in patients with a stroke or TIA, because the genetic variation reduces the activation of clopidogrel. No negative clinical consequences have been proved in other patients.

- **PERCUTANEOUS CORONARY INTERVENTION, STROKE or TIA:**
  - avoid clopidogrel
  - Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent).

- **OTHER INDICATIONS:**
  - determine the level of inhibition of platelet aggregation by clopidogrel
  - consider an alternative in poor responders

Prasugrel and ticagrelor are not metabolised by CYP2C19 (or to a lesser extent).

### Literature

31. FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. 03-12-10.

**CYP2C19 UM: clopidogrel**

NO action is required for this gene-drug interaction.

The genetic variation results in increased conversion of clopidogrel to the active metabolite. However, this can result in both positive effects (reduction in the risk of serious cardiovascular and cerebrovascular events) and negative effects (increase in the risk of bleeding).
Literature:


Date 23-12-2019

CYP1A2 IM: clozapine

This is NOT a gene-drug interaction.

Literature:


Date 13-09-2021

CYP1A2 NM: clozapine

This is NOT a gene-drug interaction.

Literature:

9. Viikki M et al. CYP1A2 polymorphism -1545C > T (rs2470890) is associated with increased side effects to clozapine. BMC Psychiatry 2014;14:50.

Date 13-09-2021

CYP1A2 PM: clozapine

This is NOT a gene-drug interaction.

Literature:

Date 13-09-2021

CYP1A2*1A/*1F: clozapine

This is NOT a gene-drug interaction.
Literature:
9. Völker M et al. CYP1A2 polymorphism -1545C > T (rs2470890) is associated with increased side effects to clozapine. BMC Psychiatry 2014;14:50.

Date 13-09-2021

CYP1A2*1C-heterozygoot: clozapine

This is NOT a gene-drug interaction.

Date 13-09-2021

CYP1A2*1C: clozapine

This is NOT a gene-drug interaction.

Date 13-09-2021

CYP2D6 IM: clozapine

NO action is required for this gene-drug interaction.

The genetic variation results in a slightly elevated plasma concentration of clozapine, but there are no clinical consequences.

Literature:
The genetic variation has a small effect on the plasma concentration of clozapine, but there are no clinical consequences.

NO action is required for this gene-drug interaction.

The genetic variation results in a slightly elevated plasma concentration of clozapine, but there are no clinical consequences.

NO action is required for this gene-drug interaction.

It is not possible to offer adequately substantiated advice for dose adjustment based on the limited available literature for this phenotype.

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
   1. try a dose increase
   2. if this does not work: choose an alternative
   Do not select tramadol, as this is also metabolised by CYP2D6.
   Oxycodeone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
3. if no alternative is selected: advise the patient to report inadequate analgesia

Literature:
The genetic variation increases the conversion of codeine to morphine. This can result in reduced analgesia.

**Recommendation:**

- For COUGH:
  1. no action required
- For PAIN:
  
  It is not possible to offer adequately substantiated advice for dose adjustment based on the limited available literature for this phenotype.

  1. choose an alternative
     
     Do not select tramadol, as this is also metabolised by CYP2D6.

     Morphine is not metabolised by CYP2D6. Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.

  2. if an alternative is not an option: advise the patient to report inadequate analgesia.

**Literature:**


8. SPC Codeinefosfaat Ratiopharm.

9. SPC Codeinefosfaat Ratiopharm.

10. It is not possible to offer adequately substantiated advice for dose adjustment based on the limited available literature for this phenotype.

11. For COUGH:

   - no action required

12. For PAIN:

   - if possible, select an alternative

   ■ For PAIN: do not select tramadol, as this is also metabolised by CYP2D6.

   Morphine is not metabolised by CYP2D6. Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.

   ■ For COUGH: noscapine is not metabolised by CYP2D6.

13. DOSES LOWER THAN OR EQUAL TO 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND NO ADDITIONAL RISK FACTORS, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:

   - no action required

**Literature:**


8. SPC Codeinefosfaat Ratiopharm.

9. SPC Codeinefosfaat Ratiopharm.

10. SPC Codeinefosfaat Ratiopharm.
**CYP2D6 IM: disopyramide**

This is NOT a gene-drug interaction.

Literature:

**Date 24-08-2016**

**CYP2D6 PM: disopyramide**

This is NOT a gene-drug interaction.

Literature:

**Date 24-08-2016**

**CYP2D6 UM: disopyramide**

This is NOT a gene-drug interaction.

Literature:

**Date 24-08-2016**

**CYP2C19 IM: doxepine**

NO action is required for this gene-drug interaction.

The gene variation has an effect on the exposure to doxepin, but not on the exposure to doxepin + the active metabolite nordoxepin, which determines the effect and side effects.

Literature:


**Date 04-03-2019**

**CYP2C19 PM: doxepine**

NO action is required for this gene-drug interaction.

The gene variation has an effect on the exposure to doxepin, but not on the exposure to doxepin + the active metabolite nordoxepin, which determines the effect and side effects.

Literature:

2. SmPC Silenor (VS).

**Date 04-03-2019**

**CYP2C19 UM: doxepine**

NO action is required for this gene-drug interaction.

The gene variations have an effect on the exposure to doxepin, but not on the exposure to doxepin + the active metabolite nordoxepin, which determines the effect and side effects.

Literature:

CYP2D6 IM: doxepine 2015

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of doxepin and the active metabolite nordoxepin.

- use 80% of the standard dose and monitor the effect and side effects or the plasma concentrations of doxepin and nordoxepin in order to set the maintenance dose
  The therapeutic range is 100-250 ng/mL for the sum of doxepin and nordoxepin plasma concentrations. Values higher than 400 ng/mL are considered toxic.

Literature:

CYP2D6 PM: doxepine 2016

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of doxepin and the active metabolite nordoxepin.

- use 40% of the standard dose and monitor the effect and side effects or the plasma concentrations of doxepin and nordoxepin in order to set the maintenance dose
  The therapeutic range is 100-250 ng/mL for the sum of doxepin and nordoxepin plasma concentrations. Values higher than 400 ng/mL are considered toxic.

Literature:
6. SmPC Silenor (VS).

CYP2D6 UM: doxepine 2017

The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of doxepin and the active metabolite nordoxepin and an increase in the plasma concentrations of the potentially cardiotoxic hydroxy metabolites.

- double the standard dose and monitor the effect and side effects or the plasma concentrations of doxepin and nordoxepin in order to set the maintenance dose
  The therapeutic range is 100-250 ng/mL for the sum of doxepin and nordoxepin plasma concentrations. Values higher than 400 ng/mL are considered toxic.
- if a dose increase is not wanted due to the potentially cardiotoxic hydroxy metabolites: avoid doxepin.
  Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Literature:

CYP2D6 IM: duloxetine 1673

This is NOT a gene-drug interaction.

Literature:

CYP2D6 PM: duloxetine 1674

This is NOT a gene-drug interaction.

Literature:
3. SPC Cymbalta.
Compliance improves with administration of a combination preparation and the absence of unnecessary side effects due to excessive plasma concentrations.

reductions did not reduce the efficacy (HIV remained undetectable), but side effects did reduce in 24 PM patients.

patients (2 of the 3 studies performed in Africa and 1 study in the United States and Italy).

The median or mean plasma concentrations or AUC in PM patients are above the therapeutic range, except in 3 studies with low efavirenz plasma concentrations in EM patients (2 of the 3 studies performed in Africa and 1 study in the United States and Italy). A recent study showed a similar virological response for efavirenz 400 and 600 mg/day in patients not selected on genotype. The risk of underdose is therefore very small if the initial dose is reduced to 400 mg/day. Two small studies showed that dose reductions did not reduce the efficacy (HIV remained undetectable), but side effects did reduce in 24 PM patients.

Compliance improves with administration of a combination preparation and the absence of unnecessary side effects due to excessive plasma concentrations.
Consideration to CYP2B6 inducers such as rifampicin is not needed in PM patients. The significantly low or absent metabolic capacity of CYP2B6 makes induction of little to no relevance. Moreover, the effects of enzyme induction by rifampicin and enzyme inhibition by isoniazid on efavirenz plasma concentrations seem to largely cancel each other out, independent of the CYP2B6 phenotype of the patient.

Literature:

20. SPC’s Efavirenz Mylan en Sustiva (VS).

Date 05-03-2018

CYP2B6*1/*5: efavirenz

NO action is required for this gene-drug interaction.

Gene variant *5 has no effect on the metabolism and consequently on the efficacy and side effects of efavirenz.

Literature:


Date 05-03-2018

CYP2B6*5/*5: efavirenz

NO action is required for this gene-drug interaction.

Gene variant *5 has no effect on the metabolism and consequently on the efficacy and side effects of efavirenz.

Literature:


Date 05-03-2018

CYP2B6*5/*6 or *5/*18: efavirenz

The genetic variation increases the plasma concentration of efavirenz and thereby the risk of side effects. However, the efavirenz plasma concentration remains within the therapeutic range for the majority of patients.

Recommendation:

- Determine the efavirenz plasma concentration if side effects occur and reduce the dose if needed.

In 14 adults with a genotype with the same effect, a reduction of the dose to 400 mg/day (2/3 of the standard dose) was sufficient to achieve therapeutic plasma concentrations and for the side effects to reduce or disappear.

The therapeutic range established for efavirenz is 1000-4000 ng/mL.

Literature:
CYP2D6 IM: eliglustat

This gene variation reduces the conversion of eliglustat to inactive metabolites. However, in the absence of CYP2D6 and CYP3A inhibitors, this does not result in a clinically significant increased risk of side effects.

Recommendation:

- Co-medication with BOTH a MODERATE to STRONG CYP2D6 INHIBITOR and a MODERATE to STRONG CYP3A INHIBITOR:
  - Eliglustat is contra-indicated.
  - Choose an alternative if possible
  
  Strong CYP2D6 inhibitor: for example paroxetine, fluoxetine, quinidine, bupropion.
  
  Moderate CYP2D6 inhibitor: for example duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone.
  
  Strong CYP3A inhibitor: for example ketonazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir.

- Choose a moderate CYP2D6 inhibitor: for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aperpitant, atazanavir, darunavir, fosamprenavir, imatinib, cerdulina.

- Co-medication with a STRONG CYP3A INHIBITOR (e.g. paroxetine, fluoxetine, quinidine, bupropion):
  - Use a dose of 84 mg eliglustat 1x daily
  - Be alert to side effects
  - Consider a dose of 84 mg eliglustat 1x daily

- Co-medication with a STRONG CYP3A INHIBITOR (for example ketonazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir):
  - Choose an alternative if possible
  - If no alternative is not an option:
    - Consider a dose of 84 mg eliglustat 1x daily
    - Be alert to side effects

- Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aperpitant, atazanavir, darunavir, fosamprenavir, imatinib, cerdulina):
  - Choose an alternative if possible
  - Be alert to side effects

- No co-medication with a moderate or strong CYP2D6 or CYP3A inhibitor or strong CYP3A inducer:
  - Use the standard dose of 84 mg 2x daily

Literature
1. SPC’s Cerdelga (Nederland en VS).

Date 05-03-2018

CYP2D6 PM: eliglustat

This gene variation reduces the conversion of eliglustat to inactive metabolites. This increases the risk of side effects, such as a (small, dose-dependent) elongation of the QT interval. CYP3A inhibitors increase this risk even further.

Recommendation:

- Co-medication with a STRONG CYP3A INHIBITOR (for example ketonazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir):
  - Eliglustat is contra-indicated.
  - Use the standard dose of 84 mg eliglustat 1x daily

- Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aperpitant, atazanavir, darunavir, fosamprenavir, imatinib, cerdulina):
  - Eliglustat is not recommended. The plasma concentration may decrease so sharply that a therapeutic effect cannot be achieved.
  - Choose an alternative if possible

Literature
1. SPC’s Cerdelga (Nederland en VS).

Date 31-10-2016
2. be alert to side effects
   • Co-medication with a STRONG CYP3A INDUCER (for example rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutine, hypericum):
     Eliglustat is not recommended. The plasma concentration may decrease so sharply that a therapeutic effect cannot be achieved.
     1. choose an alternative if possible
   • NO co-medication with a CYP3A inhibitor or strong CYP3A inducer:
     1. use a dose of 84 mg 1x daily

Literature:
1. SPC’s Cerdelga (Nederland en VS).

Date 31-10-2016

CYP2D6 UM: eliglustat

This gene variation increases the conversion of eliglustat to inactive metabolites. As a result, a normal dose is not effective. There is not enough scientific substantiation to suggest an effective dose for all UM.

Recommendation:
Eliglustat is contra-indicated.
1. choose an alternative if possible

Literature:
1. SPC’s Cerdelga (Nederland en VS).

Date 31-10-2016

CYP2C19 IM: escitalopram

The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased escitalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset.

- Do not exceed the following doses (75% of the standard maximum dose):
  - adults < 65 years 15 mg/day, ≥65 years 7.5 mg/day

Literature:

Date 14-05-2018

CYP2C19 PM: escitalopram

The risk of switching to another antidepressant is increased. In addition, the risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased escitalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration, the theoretically increased risk of QT prolongation and the increased risk of switching to another antidepressant will be offset.

- Do not exceed the following doses (50% of the standard maximum dose):
  - adults < 65 years 10 mg/day, ≥65 years 5 mg/day

Literature:
8. Waade RB et al. Impact of age on serum concentrations of venlafaxine and escitalopram in different CYP2D6 and CYP2C19 genotype subgroups. Eur J Clin Pharmacol
CYP2C19 UM: escitalopram

The risk of switching to another antidepressant is increased as the gene variation leads to a reduction in the escitalopram plasma concentration.

- avoid escitalopram

Antidepressants that are not metabolised or that are metabolised to a lesser extent by CYP2C19 are, for example, paroxetine or fluvoxamine.

Literature:

9. SPC's Lexapro (NL/en VS).

CYP2C19 IM: esomeprazole

NO action is needed for this gene-drug interaction.

Although the genetic variation leads to a higher plasma concentration of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

Literature:

4. Ng C et al. Pharmacogenetic polymorphisms lead to a higher plasma concentration of some prazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and treatment response. Pharmacogenomics 2010;11:537-46.

CYP2C19 PM: esomeprazole

NO action is needed for this gene-drug interaction.

Although the genetic variation leads to a higher plasma concentration of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

Literature:


Date 05-03-2018

CYP2C19 PM: esomeprazole

NO action is needed for this gene-drug interaction.

Although the genetic variation leads to a higher plasma concentration of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

Literature:


14. SPC Nexit (Nederlands en Amerikaans).

Date 05-03-2018

CYP2C19 UM: esomeprazole

NO action is required for this gene-drug interaction.

Although the genetic variation may lead to faster inactivation of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

Literature:


Date 05-03-2018

CYP2C9 IM ANDERS: fenprocoumon

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

Literature:


The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e., frequent INR monitoring).

**Literature:**

**Date 14-05-2018**

**CYP2C9*1/*2: fenprocoumon**

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e., frequent INR monitoring).

**Literature:**

**Date 14-05-2018**

**CYP2C9*1/*3: fenprocoumon**

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e., frequent INR monitoring).

**Literature:**
872

CYP2C9*2: fenprocoumon

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

CYP2C9*3: fenprocoumon

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

CYP2C9*2 and CYP2C9*3: fenprocoumon

NO action is required for both gene-drug interactions.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

CYP2C9*2 and CYP2C9*3: fenprocoumon

NO action is required for both gene-drug interactions.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

CYP2C9*2 and CYP2C9*3: fenprocoumon

NO action is required for both gene-drug interactions.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).
CYP2C9*3/*3: fenprocoumon

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose. However, there is not enough evidence to confirm that this causes problems with normal initiation of the therapy (i.e. frequent INR monitoring).

Literature:


For patients younger than 75 years, the initial dose and the maintenance dose can be calculated using an algorithm as found in EU-PACT: see https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica for a calculation tool in the form of an Excel file. However, for patients aged 75 years and older, this algorithm increases the risk of an INR above the therapeutic range compared to an algorithm without gene variations. Therefore, use of this algorithm is not recommended for these patients.

Date 14-05-2018

VKORC1 -1639 AA: fenprocoumon

An INR ≥ 6, resulting in an increased risk of bleeding, occurs in 17% of these patients with standard regulation by the Anticoagulation Clinic. The genetic variation increases the sensitivity to phenprocoumon.

- Monitoring by an ANTICOAGULATION CLINIC:
  - recommend to use 50% of the standard initial dose
- NO monitoring by a anticoagulation clinic:
  - recommend to use 50% of the standard initial dose
  - recommend more frequent monitoring of the INR

For patients younger than 75 years, the initial dose and the maintenance dose can be calculated using an algorithm as found in EU-PACT: see https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica for a calculation tool in the form of an Excel file. However, for patients aged 75 years and older, this algorithm increases the risk of an INR above the therapeutic range compared to an algorithm without gene variations. Therefore, use of this algorithm is not recommended for these patients.

Literature:


VKORC1 -1639 GA: fenprocoumon

NO action is needed for this gene-drug interaction.

The gene variation leads to a lower dose requirement, but regular monitoring of patients ensures that this does not lead to a distinct increase in the risk of bleeding.

Literature:


Date 10-09-2018

VKORC1 -1639 GA: fenprocoumon

NO action is needed for this gene-drug interaction.

The gene variation leads to a lower dose requirement, but regular monitoring of patients ensures that this does not lead to a distinct increase in the risk of bleeding.

Literature:


Literature:


Date 10-09-2018

CYP2C9 IM ANDERS: fenitoin

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.

Recommendation:
1. The loading dose does not need to be adjusted.
2. For the other doses, use 75% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Literature:


Date 31-10-2016

CYP2C9 PM ANDERS: fenitoin

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.

Recommendation:
1. The loading dose does not need to be adjusted.
2. For the other doses, use 40-50% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Literature:


Date 31-10-2016

CYP2C9*1/*2: fenitoin

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.

Recommendation:
1. The loading dose does not need to be adjusted.
2. For the other doses, use 50-75% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Literature:

Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. The life-threatening cutaneous side effects Stevens-Johnson Syndrome and toxic epidermal necrolysis may occur, especially in Asian patients.

Recommendation:
1. The loading dose does not need to be adjusted.
2. For the other doses, use 75% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or, especially in Asian patients, rash) occur.

Literature:
15. www.nvza.nl, TDM monografie voor fenitoin.
The life-threatening cutaneous side effect Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) occurs more frequently in patients with this genetic variation. The Syndrome and toxic epidermal necrolysis may occur, especially in Asian patients. Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. The life-threatening cutaneous side effects Stevens-Johnson Syndrome and toxic epidermal necrolysis may occur, especially in Asian patients.

Recommendation:
1. The loading dose does not need to be adjusted.
2. For the other doses, use 40% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.

Literature:
15. www.nvza.nl, TDM monografie voor fenitoin.

Date 31-10-2016

CYP2C9*3/3: fenitoine

Recommendation:
1. The loading dose does not need to be adjusted.
2. For the other doses, use 40% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
3. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or, especially in Asian patients, rash) occur.

Literature:
10. SmPC Diphantoïne-Z.
11. SmPC Dilantin (VS).

Date 14-05-2018

CYP2D6 IM: flecainide
The genetic variation reduces conversion of flecainide to inactive metabolites. This may increase the risk of side effects.

**Recommendation:**

- Indications other than diagnosis of Brugada syndrome:
  1. reduce the dose to 75% of the standard dose and record an ECG and monitor the plasma concentration
- Provocation test for diagnosis of Brugada syndrome:
  No action required.

At a dose of 2.0 mg/kg body weight to a maximum of 150 mg, the response is better for patients with alleles that result in reduced activity. All 5 patients with these alleles and 20% of the patients with two fully active alleles exhibited a response within 30 minutes.

**Literature:**


The genetic variation increases conversion of flecainide to inactive metabolites. A higher dose is possibly required as a result.

**Recommendation:**

There are no data about the pharmacokinetics and/or the effects of flecainide in UM.

- monitor the plasma concentration as a precaution and record an ECG or select an alternative
- Examples of anti-arrhythmic drugs that are not metabolised via CYP2D6 (or to a lesser extent) include sotalol, disopyramide, quinidine and amiodarone.

**Literature:**


**HLA-B*5701: flucloxacilline**

**Recommendation:**

- Regularly monitor the patient’s liver function
- Choose an alternative if liver enzymes and/or bilirubin levels are elevated

**Literature:**

3. Daly AK et al. HLA-B*5701 genotype is a major determinant of drug induced liver injury due to flucloxacillin. Nature Genetics 2009;41:816-9.
4. SmPC Floxapen.

**DPD AS 0: flucytosine**

A risk of life-threatening toxicity is increased by gene variation. A small proportion of flucytosine is converted to fluorouracil and patients with this gene variation are intolerant even to small quantities of fluorouracil.
Avoid flucytosine

Literature:
2. SmPC Ancotil.

Date 14-09-2020

DPD AS 1.5: flucytosine

A very low risk of severe toxicity is increased by gene variation. A small proportion of flucytosine is converted to fluorouracil. Patients with this gene variation are more likely to have a reaction to fluorouracil, but generally tolerate low doses (50-75% of the standard fluorouracil dose). Be alert to the occurrence of severe side effects, such as leukopenia, neutropenia, thrombocytopenia and diarrhea.
In the majority of cases, side effects of flucytosine occur in the first two to three weeks of the treatment. Flucytosine should be stopped if severe side effects occur.

Literature:
2. SmPC Ancotil.

Date 14-09-2020

DPD AS 1: flucytosine

A very low risk of severe toxicity is increased by gene variation. A small proportion of flucytosine is converted to fluorouracil. Patients with this gene variation are more likely to react to fluorouracil, but generally tolerate low doses (approximately 50% of the standard fluorouracil dose). Be alert to the occurrence of severe side effects, such as leukopenia, neutropenia, thrombocytopenia and diarrhea.
In the majority of cases, side effects of flucytosine occur in the first two to three weeks of the treatment. Flucytosine should be stopped if severe side effects occur.

Literature:
2. SmPC Ancotil.

Date 14-09-2020

DPD FENO: flucytosine

A very low risk of severe toxicity is increased by gene variation. A small proportion of flucytosine is converted to fluorouracil. Patients with this gene variation are more likely to have a reaction to fluorouracil, but generally tolerate low doses (15-50% of the standard fluorouracil dose). Be alert to the occurrence of severe side effects, such as leukopenia, neutropenia, thrombocytopenia and diarrhea.
In the majority of cases, side effects of flucytosine occur in the first two to three weeks of the treatment. Flucytosine should be stopped if severe side effects occur.

Literature:
2. SmPC Ancotil.

Date 14-09-2020

DPD AS 0: fluorouracil cutaan

The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

Avoid fluorouracil

NOTE: If a patient has two different genetic variations that lead to a non-functional DPD enzyme (e.g. *2A and *13), this recommendation only applies if the variations are on a different allele. If both variations are on the same allele, this patient actually has a gene activity score 1, for which no increased risk of severe, potentially fatal toxicity has been found with cutaneous use. These two situations can only be distinguished by determining the enzyme activity (phenotyping). This recommendation only applies if the patient has virtually no enzyme activity.

Literature:
15. SPC Euficix crème en Carac cream (VS).

Date 13-05-2019

**DYPD AS 1.5: fluorouracil/capecitabine**

The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

- Start with 50% of the standard dose or avoid fluorouracil and capecitabine.
- Adjustment of the subsequent dose should be guided by toxicity and effectiveness. However, in one study involving 17 patients with gene polymorphism 1, the average dose after titration was 57% of the standard dose. Tegafur is not an alternative, as this is also metabolised by DYPD.

**Literature:**

22. SPC Euficix crème en Carac cream (VS).
The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose of these drugs is adequate for patients with dihydropyrimidine dehydrogenase gene variation. The benefit could be larger in patients with a c.1129-5923C>G haplotype B3 who have partial DPD deficiency and require a dose reduction when treated with fluoropyrimidines.

References:
17. SPC's Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS) en Xeloda (VS).

Date 13-05-2019

DPD FENO: fluorouracil/capecitabine

The gene variation increases the risk of the severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the normal dose is an overdose.

It is not possible to recommend a dosage adjustment for this patient based on the genotype only.

- determine the residual DPD activity in mononuclear cells from peripheral blood and adjust the initial dose based on phenotype and genotype, or avoid fluorouracil and capecitabine.
- Testafal is not an alternative, as this is also metabolised by DPD.

References:
2. Lunnunenburg CA et al. Standard DPD dosages in chemoradiation therapy result in an increased risk of severe toxicity in DPD variant allele carriers. Eur J Cancer 2018;142:0.
DPD AS 0: fluorouracil/capecitabine, systemisch

The gene variation increases the risk of severe, potentially fatal toxicity. A reduced conversion of fluorouracil/capecitabine to inactive metabolites means that the standard dose is a more than 100-fold overdose.

- Avoid fluorouracil and capecitabine
  - Tegafur is not an alternative, as this is also metabolised by DPD.
- If it is not possible to avoid fluorouracil and capecitabine: determine the residual DPD activity in mononuclear cells from peripheral blood and adjust the initial dose accordingly.

A patient with 0.5% of the normal DPD activity tolerated 0.8% of the standard dose (150 mg capecitabine every 5 days). A patient with undetectable DPD activity tolerated 0.43% of the standard dose (150 mg capecitabine every 5 days with every third dose skipped)

Literature:

16. SPC’s Fluorouracil PCH, Xeloda, Efudix creme, Fluorouracil (VS), Xeloda (VS) en Carac cream (VS).

CYP2D6 IM: fluoxetine

NO action is needed for this gene-drug interaction.

The ratio of fluoxetine/norfluoxetine increases as a result of the reduced activity of CYP2D6. However, this does not affect the sum of the plasma concentrations of the active substances (fluoxetine and norfluoxetine). There is no effect on adverse events or response.

Literature:


CYP2D6 PM: fluoxetine

NO action is needed for this gene-drug interaction.

The ratio of fluoxetine/norfluoxetine increases as a result of the reduced activity of CYP2D6. However, this does not affect the sum of the plasma concentrations of the active substances (fluoxetine and norfluoxetine). There is insufficient evidence to support an effect on adverse events or response.

Literature:

5. Roberts RL et al. No evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolizers treated with fluoxetine or norflouptin. Hum Psychopharmacol 2004;19:17-23.
7. SPC Prazac, USA, 30-01-09.
CYP2D6 UM: fluoxetine

NO action is needed for this gene-drug interaction.

The ratio of fluoxetine/norfluoxetine decreases as a result of the increased activity of CYP2D6. However, this does not affect the sum of the plasma concentrations of the active substances (fluoxetine and norfluoxetine). There is no effect on adverse events or response.

Literature:

CYP2D6 IM: flupentixol

This is NOT a gene-drug interaction.

Literature:

CYP2D6 PM: flupentixol

This is NOT a gene-drug interaction.

Literature:

CYP2D6 UM: flupentixol

This is NOT a gene-drug interaction.

Literature:

SLCO1B1 521CC: fluvastatine

NO action is required for this gene-drug interaction.

The gene variation increases the plasma concentration of fluvastatin, but there is insufficient evidence to prove an effect on efficacy or side effects.

Literature:
The gene variation increases the plasma concentration of fluvastatin, but there is insufficient evidence to prove an effect on efficacy or side effects.

Literature:

Date 14-05-2018

CYP2D6 PM: fluvoxamine

NO action is needed for this gene-drug interaction.

The plasma concentration of fluvoxamine can increase as a result of the reduced activity of CYP2D6. However, there is no scientific substantiation of a reduced effectiveness.

Literature:

1. Christensen M et al. Low daily 10-mg and 20-mg doses of fluvoxamine inhibit the metabolism of both caffeine (cytochrome P4501A2) and omeprazole (cytochrome P4502C19). Clin Pharmacol Ther 2002;71:141-52.
4. SPC's Fervarin en Luvox (VS).
The only relevant clinical consequence that was found is an increased effectiveness of glibenclamide without an increase in the frequency and severity of hypoglycaemia.

NO action is required for this gene-drug interaction.

Literature:

Date 07-06-2021

CYP2D6 IM: gefitinib

NO action is needed for this gene-drug interaction.

Side effects can occur more frequently, as the gene variation increases the gefitinib plasma concentration. However, the side effects are reversible and manageable, to an extent that adjustment of the therapy in advance is not necessary.

Literature:

Date 19-11-2018

CYP2D6 PM: gefitinib

NO action is needed for this gene-drug interaction.

The gefitinib plasma concentration may increase due to reduced CYP2D6 activity. However, there is no evidence to suggest that side effects increase to an extent that adjustment of therapy is needed.

Literature:
3. SPC Iressa.

Date 19-11-2018

CYP2D6 UM: gefitinib

NO action is needed for this gene-drug interaction.

The gene variation may lead to a decrease in the gefitinib plasma concentration. In practice, an alternative is only chosen if non-response to gefitinib has been proved. Moreover, dose adjustments guided by the gefitinib plasma concentration are rarely performed in clinical practice as the analytical method is not available in most hospitals.

Literature:
3. SPC Iressa.

Date 19-11-2018

CYP2C9 IM ANDERS: glibenclamide

NO action is required for this gene-drug interaction.

The only relevant clinical consequence that was found is an increased effectiveness of glibenclamide without an increase in the frequency and severity of hypoglycaemia.

Literature:

Date 20-11-2017

CYP2C9 PM ANDERS: glibenclamide

NO action is required for this gene-drug interaction.

No relevant clinical consequences have been found for the genetic variation.

Literature:

Date 20-11-2017

CYP2C9*1/*2: glibenclamide

NO action is required for this gene-drug interaction.

The only relevant clinical consequence that was found is an increased effectiveness of glibenclamide without an increase in frequency and severity of hypoglycaemia for a group of 1 *1/*2 and 15 *1/*3.

Literature:

Date 20-11-2017

CYP2C9*1/*3: glibenclamide

NO action is required for this gene-drug interaction.

The only relevant clinical consequence is an increased effectiveness of glibenclamide without an increase in frequency and severity of hypoglycaemia.

Literature:

Date 20-11-2017

CYP2C9*2/*2: glibenclamide

NO action is required for this gene-drug interaction.

No significant clinical consequences have been found for the genetic variation.

Literature:

Date 20-11-2017

CYP2C9*2/*3: glibenclamide

NO action is required for this gene-drug interaction.

No significant kinetic or clinical consequences have been found for this genetic variation.
Literature:


Date 20-11-2017

CYP2C9*3/*3: glibenclamide

NO action is required for this gene-drug interaction.
No relevant clinical consequences have been found for this genetic variation.

Literature:


Date 20-11-2017

CYP2C9 IM ANDERS: gliclazide

NO action is required for this gene-drug interaction.
The genetic variation increases the effectiveness of gliclazide without significantly increasing the risk of hypoglycaemia.

Literature:


Date 20-11-2017

CYP2C9 PM ANDERS: gliclazide

NO action is required for this gene-drug interaction.
The genetic variation increases the effectiveness of gliclazide without significantly increasing the risk of hypoglycaemia.

Literature:


Date 20-11-2017

CYP2C9*1/*2: gliclazide

NO action is required for this gene-drug interaction.
The genetic variation increases the effectiveness of gliclazide.

Literature:


Date 20-11-2017

CYP2C9*1/*3: gliclazide

NO action is required for this gene-drug interaction.
The genetic variation increases the effectiveness of gliclazide without significantly increasing the risk of hypoglycaemia.

Literature:
NO action is required for this gene-drug interaction.
The genetic variation increases the effectiveness of gliclazide without significantly increasing the risk of hypoglycaemia.

Literature:
Literature:


Date 20-11-2017

CYP2C9 PM ANDERS: glimepiride

NO action is required for this gene-drug interaction.

Although the genetic variation increases the risk of hypoglycaemia, this risk remains low. This also means that the genetic variation increases the effectiveness. A lack of effectiveness is a much more common problem with sulphonyl urea derivatives than the occurrence of hypoglycaemia.

Date 20-11-2017

CYP2C9*1/*2: glimepiride

NO action is required for this gene-drug interaction.

No significant kinetic or clinical consequences have been found for the genetic variation.

Date 20-11-2017

CYP2C9*1/*3: glimepiride

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of glimepiride.

Date 20-11-2017

CYP2C9*2/*2: glimepiride

NO action is required for this gene-drug interaction.

No significant clinical effects were observed for this genetic variation.

Date 20-11-2017

CYP2C9*2/*3: glimepiride

NO action is required for this gene-drug interaction.

No significant clinical effects were observed for this genetic variation.


CYP2C9*2/*3: glimepiride

NO action is required for this gene-drug interaction.

Although the genetic variation increases the risk of hypoglycaemia, this risk remains low. This also means that the genetic variation increases the effectiveness. A lack of effectiveness is a much more common problem with sulphonyl urea derivatives than the occurrence of hypoglycaemia.

Literature:

CYP2D6 IM: haloperidol

NO action is required for this gene-drug interaction.

The genetic variation results in a higher plasma concentration, but the effect is small and no clinically significant effects were found.

Literature:

CYP2D6 PM: haloperidol

There are indications for an increased risk of side effects. The genetic variation leads to decreased conversion of haloperidol, resulting in plasma concentrations that are approximately 1.7-fold higher.

- use 60% of the standard
The risk of side effects is increased. The genetic variation results in an increase in the plasma concentration of imipramine+desipramine.

- use 70% of the standard dose and monitor the effect and side effects, or the imipramine and desipramine plasma concentrations to determine the maintenance dose.
- or avoid imipramine

Antidepressants that are not or to a lesser extent metabolised by CYP2C19 include, for example, nortriptyline, fluvoxamine and mirtazapine.

Literature:
Literature:


Date 10-09-2018

**CYP2C19 UM: imipramine**

NO action is required for this gene-drug interaction.

The genetic variation decreases imipramine plasma concentrations, but not imipramine+desipramine plasma concentrations, which govern effectiveness and side effects.

Literature:


Date 10-09-2018

**CYP2D6 IM: imipramine**

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of imipramine and desipramine.

- use 70% of the standard dose and monitor the effect and side effects or the plasma concentrations of imipramine and desipramine in order to set the maintenance dose
- The therapeutic range is 150-300 ng/mL for the sum of the imipramine and desipramine plasma concentrations. Values exceeding 500 ng/mL are considered toxic.

Literature:


Date 11-09-2018

**CYP2D6 PM: imipramine**

The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of imipramine and the active metabolite desipramine.

- use 30% of the standard dose and monitor the effect and side effects or the plasma concentrations of imipramine and desipramine in order to set the maintenance dose
- The therapeutic range is 150-300 ng/mL for the sum of the imipramine and desipramine plasma concentrations. Values exceeding 500 ng/mL are considered toxic.

Literature:


Date 11-09-2018

**CYP2D6 UM: imipramine**

The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of imipramine and the active metabolite desipramine and to increased plasma concentrations of the potentially cardiotoxic hydroxy metabolites.

- use 1.7 times the standard dose and monitor the effect and side effects or the plasma concentrations of imipramine and desipramine in order to set the maintenance dose
- if a dose increase is not wanted due to the potentially cardiotoxic hydroxy metabolites: avoid imipramine.
- Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.

Literature:

This genetic variation (IM) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.

Literature:
1. Yang Y et al. UGT1A16 and UGT1A128 polymorphisms are correlated with irinotecan-induced toxicity: A meta-analysis. Asia Pac J Clin Oncol 2018;14:e479-e489.

Date 07-06-2021

UGT1A1 PM ANDERS: irinotecan
Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites.

- Start with 70% of the standard dose
- If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

Literature:
1. Yang Y et al. UGT1A16 and UGT1A128 polymorphisms are correlated with irinotecan-induced toxicity: A meta-analysis. Asia Pac J Clin Oncol 2018;14:e479-e489.

Date 07-06-2021

UGT1A1*1/*28: irinotecan
NO action is needed for this gene-drug interaction.

This genetic variation (*1/*28) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.

Literature:
1. Yang Y et al. UGT1A16 and UGT1A128 polymorphisms are correlated with irinotecan-induced toxicity: A meta-analysis. Asia Pac J Clin Oncol 2018;14:e479-e489.
Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites.

- Start with 70% of the standard dose
- If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

**Literature:**

1. Yang Y et al. UGT1A1 and UGT1A2 polymorphisms are correlated with irinotecan-induced toxicity: A meta-analysis. Asia Pac J Clin Oncol 2018;14:e479-489.

**Date 07-06-2021**
The higher plasma concentration of lansoprazole results in an increase in the therapeutic effectiveness, without an increase in the incidence of side effects.

**Literature**


**CYP2C19 PM: lansoprazole**

NO action is needed for this gene-drug interaction.

The higher plasma concentration of lansoprazole results in an increase in the therapeutic effectiveness, without an increase in the incidence of side effects.

**Literature**


Recommendation:
The genetic variation may reduce lansoprazole plasma concentrations and therefore lansoprazole effectiveness.

Date 05-03-2018

1833


41. SPC Prezal.

Date: 05-03-2018

**MTHFR 677C: methotrexat**

This is NOT a gene-drug interaction.

**Literature:**


Date: 07-06-2021

**MTHFR 677T: methotrexat**

This is NOT a gene-drug interaction.

**Literature:**


**Date 07-06-2016**

**Comt met/met: methylfenidaat**

This is NOT a gene-drug interaction.

**Literature:**


**Date 01-05-2017**

**Comt val/met: methylfenidaat**

This is NOT a gene-drug interaction.

**Literature:**


**Date 01-05-2017**

**CYP2D6 IM: methylfenidaat**

This is NOT a gene-drug interaction.

**Literature:**


**Date 24-08-2016**

**CYP2D6 PM: methylfenidaat**

This is NOT a gene-drug interaction.

**Literature:**

CYP2D6 UM: methylenidate
This is NOT a gene-drug interaction.

Date 24-08-2016

CYP2D6 IM: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 50% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 PM: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 UM: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 VM: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 SM: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 HM: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 LW: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 MN: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 MW: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 NW: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 OW: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 PV: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 QW: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 VW: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 WX: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 XY: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016

CYP2D6 ZZ: metoprolol

The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.

Recommendation:

- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  1. use smaller steps in dose titration and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Date 25-05-2016
CYP2D6 UM: metoprolol

The gene variation increases the conversion of metoprolol to inactive metabolites. This can increase the dose requirement. However, with a target dose of 200 mg/day, there was no effect on the blood pressure and hardly any effect on the reduction of the heart rate.

Recommendation:

1. use the maximum dose for the relevant indication as a target dose
2. if the effectiveness is still insufficient: increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative

Possible alternatives include:
- HEART FAILURE: bisoprolol or carvedilol. Bisoprolol: advantage: not metabolised by CYP2D6; disadvantage: elimination depends on the kidney function. Carvedilol: advantage: elimination does not depend on the kidney function; disadvantage: is metabolised (to a lesser extent than metoprolol) by CYP2D6.
- OTHER INDICATIONS: atenolol or bisoprolol. Neither is metabolised by CYP2D6.

Literature:

2. Goryachkina K et al. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. Eur J Clin Pharmacol 2008;64:1163-73.

Date 25-05-2016

CYP2C19 IM: mirtazapine

This is NOT a gene-drug interaction.

Literature:


Date 10-09-2018

CYP2C19 PM: mirtazapine

This is NOT a gene-drug interaction.

Literature:


Date 10-09-2018

CYP2C19 UM: mirtazapine

This is NOT a gene-drug interaction.

Literature:


Date 10-09-2018

CYP2D6 IM: mirtazapine

NO action is required for this gene-drug interaction.

There is insufficient evidence to suggest that the higher plasma concentration of mirtazapine results in an increase in the side effects or efficacy.

Literature:

CYP2D6 PM: mirtazapine

NO action is required for this gene-drug interaction.

The higher plasma concentration of mirtazapine does not result - or hardly results - in an increase in the side effects.

Literature:


CYP2D6 UM: mirtazapine

NO action is required for this gene-drug interaction.

The effect on the plasma concentration of mirtazapine is small. No effect has been demonstrated with regard to effectiveness or side effects.

Literature:


CYP2C19 IM: moclobemide

NO action is needed for this gene-drug interaction.

Although the moclobemide plasma concentration may increase as a result of the decreased CYP2C19 activity, this does not lead to an increased incidence of side effects, as far as is known.

Literature:

2. SPC Aurorix.

CYP2C19 PM: moclobemide

NO action is needed for this gene-drug interaction.

Although the moclobemide plasma concentration may increase as a result of the decreased CYP2C19 activity, this does not lead to an increased incidence of side effects, as far as is known.

Literature:

3. SPC Aurorix.
CYP2C19 UM: moclobemide

NO action is needed for this gene-drug interaction.

Although the moclobemide plasma concentration may decrease as a result of increased CYP2C19 activity, this does not lead to increased effectiveness, in as far as is known.

Literature:
2. SPC Aurorix.

CYP2D6 IM: nortriptyline

The risk of side effects may be increased, because the gene variation leads to an increased plasma concentration of nortriptyline.

- use 60% of the standard dose and monitor the effect and side effects or the plasma concentration of nortriptyline in order to set the maintenance dose

The therapeutic range of nortriptyline is 50-150 ng/mL. Values exceeding 250 ng/mL are considered toxic.

Literature:

CYP2D6 PM: nortriptyline

The risk of side effects may be increased, because the gene variation leads to an increased plasma concentration of nortriptyline.

- use 40% of the standard dose and monitor the effect and side effects or the plasma concentration of nortriptyline in order to set the maintenance dose

The therapeutic range of nortriptyline is 50-150 ng/mL. Values exceeding 250 ng/mL are considered toxic.

Literature:
4. Roberts et al. No evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolizers treated with fluoxetine or nortriptyline. Hum Psychopharmacol 2004 Jan;19:17-23.
10. SmPC Palmol (VS).

CYP2D6 UM: nortriptyline

The risk of ineffectiveness and cardiotoxic effects may be increased. The gene variation leads to a decrease in the plasma concentration of nortriptyline and an increase in the plasma concentration of the cardiotoxic metabolite Z-10-hydroxynortriptyline.

- use 1.7 times the standard dose and monitor the effect and side effects or the plasma concentration of nortriptyline and be alert to an increase in the plasma concentration of the cardiotoxic metabolite Z-10-hydroxynortriptyline

Plasma concentrations of Z-hydroxynortriptyline exceeding 40 ng/mL are considered toxic.

- if a dose increase is not wanted due to the cardiotoxic hydroxy metabolite: avoid nortriptyline

Antidepressants that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.

Literature:
CYP1A2 IM: olanzapine
This is NOT a gene-drug interaction.

Date 13-09-2021
CYP1A2 NM: olanzapine
This is NOT a gene-drug interaction.

Date 13-09-2021
CYP1A2 PM: olanzapine
This is NOT a gene-drug interaction.

Date 13-09-2021
CYP1A2*1A/*1F: olanzapine
This is NOT a gene-drug interaction.

Literature:

4. Hattori S et al. The association of genetic polymorphisms in CYP1A2, UGT1A4, and ABCB1 with autonomic nervous system dysfunction in schizophrenia patients treated with olanzapine. BMC Psychiatry 2020;20:72.
7. Czerwensky F et al. CYP1A2*1D and *1F polymorphisms have a significant impact on olanzapine serum concentrations. Ther Drug Monit 2015;37:152-60.
CYP1A2*1C-heterozygoot: olanzapine

This is NOT a gene-drug interaction.

Literature:

CYP1A2*1C/*1C: olanzapine

This is NOT a gene-drug interaction.

Literature:
2. Hatton S et al. The association of genetic polymorphisms in CYP1A2, UGT1A1, and ABCB1 with autonomic nervous system dysfunction in schizophrenia patients treated with olanzapine. BMC Psychiatry 2020;20:72.

CYP2D6 IM: olanzapine

This is NOT a gene-drug interaction.

Literature:

CYP2D6 PM: olanzapine

This is NOT a gene-drug interaction.

Literature:
CYP2D6 UM: omeprazole

This is NOT a gene-drug interaction.

Literature:


Date 13-09-2021

CYP2C19 IM: omeprazole

NO action is required for this gene-drug interaction.

The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

Literature:


Date 13-09-2021

CYP2C19 PM: omeprazole

NO action is required for this gene-drug interaction.

The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

Literature:

CYP2C19 UM: omeprazole

The genetic variation may lead to a reduced omeprazole plasma concentration and therefore reduced effectiveness.

Recommendation:

- For Helicobacter pylori ERADICATION THERAPY:
  1. use a 3-fold higher dose
  2. advise the patient to contact their doctor if symptoms of dyspepsia persist

- OTHER INDICATIONS:
  1. be alert to reduced effectiveness
  2. if necessary, use a 3-fold higher dose
  3. advise the patient to report persisting symptoms of dyspepsia

Literature:


Date 05-03-2018

CYP2C19 UM: omeprazole

The genetic variation may lead to a reduced omeprazole plasma concentration and therefore reduced effectiveness.

Recommendation:

- For Helicobacter pylori ERADICATION THERAPY:
  1. use a 3-fold higher dose
  2. advise the patient to contact their doctor if symptoms of dyspepsia persist

- OTHER INDICATIONS:
  1. be alert to reduced effectiveness
  2. if necessary, use a 3-fold higher dose
  3. advise the patient to report persisting symptoms of dyspepsia

Literature:


1841
Literature:
The reduced conversion of oxycodone to the more active metabolite oxymorphone does not result in reduced analgesia for patients. NO action is required for this gene-drug interaction.

Date 05-03-2018

HLA-B*1502: oxcarbazepine

Stevens-Johnson syndrome, the severe cutaneous side effect that can potentially result in permanent damage, occurs more often in patients with this genetic variation. The calculated risk of oxcarbazepine-induced SJS in patients with HLA-B*1502 is 0.73%.

- carefully weigh the risk of SJS against the benefits
- avoid oxcarbazepine if an alternative is available
- Carbamazepine carries a 10-fold higher risk of SJS/TEN in these patients and is therefore not an alternative.
In these patients, phenytoin and lamotrigine carry a similar risk of SJS/TEN as oxcarbazepine, but more severe forms of SJS/TEN (SJS/TEN overlap and TEN) are also observed with these medicines. Therefore, they are also not suitable as alternatives.

- if it is not possible to avoid oxcarbazepine, advise the patient to report any rash immediately

Literature:

Date 14-05-2018

CYP2D6 IM: oxycodone

NO action is required for this gene-drug interaction.

The reduced conversion of oxycodone to the more active metabolite oxymorphone does not result in reduced analgesia for patients.

Literature:
6. SmPC’s Losec en Prilosec (VS).

Date 20-11-2017

CYP2D6 PM: oxycodone

NO action is required for this gene-drug interaction.

The reduced conversion of oxycodone to the more active metabolite oxymorphone does not result in reduced analgesia in patients.

Literature:

Date 20-11-2017
CYP2D6 UM: oxycodeon

NO action is required for this gene-drug interaction.

The increased conversion of oxycodeon to the more active metabolite oxymorphone does not result in an increase in side effects in patients.

Literature:

CYP3A4 IM: paclitaxel

NO action is required for this gene-drug interaction.

The genetic variation has a slight effect on the metabolism of paclitaxel, and there is insufficient evidence of an increase in adverse events or reduced efficacy.

Literature:

CYP3A4 PM: paclitaxel

NO action is required for this gene-drug interaction.

The genetic variation has a slight effect on the metabolism of paclitaxel, and there is insufficient evidence of an increase in adverse events or reduced efficacy.

Literature:

CYP2C19 IM: pantoprazol

NO action is required for this gene-drug interaction.

The higher plasma concentration of pantoprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

Literature:

Date 05-03-2018

CYP2C19 PM: pantoprazole

NO action is required for this gene-drug interaction.

The higher plasma concentration of pantoprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

Literature:

Date 05-03-2018

CYP2C19 UM: pantoprazole

The genetic variation may lead to reduced pantoprazole plasma concentrations and therefore reduced pantoprazole effectiveness.

Recommendation:
- For Helicobacter pylori ERADICATION THERAPY:
  1. use a 5-fold higher dose
  2. advise the patient to contact their doctor if symptoms of dyspepsia persist
- OTHER INDICATIONS:
  1. be alert to reduced effectiveness
  2. if necessary, use a 5-fold higher dose
  3. advise the patient to report persisting symptoms of dyspepsia

Literature:
CYP2D6 IM: paroxetine

NO action is needed for this gene-drug interaction.

The plasma concentration of paroxetine can increase as a result of the reduced activity of CYP2D6. However, studies did not find any clinical effects.

Literature:

CYP2D6 PM: paroxetine

NO action is needed for this gene-drug interaction.

The plasma concentration of paroxetine can increase as a result of the reduced activity of CYP2D6. However, studies did not find any clinical effects.

Literature:

CYP2D6 UM: paroxetine

Efficacy will probably be lacking. The genetic variation increases the conversion of paroxetine.

It is not possible to offer substantiated advice for dose adjustment based on the literature.

- avoid paroxetine
  - Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include for example citalopram or sertraline.

Literature:
Date 14-05-2018

CYP2D6 IM: pimozide

The risk of QT-prolongation - and thereby also the risk of torsade de points - is theoretically increased, because the genetic variation results in an increase in the plasma concentration of pimozide. The elevated plasma concentration and associated theoretical increased risk of QT elongation can be negated by following the dose recommendations provided below.

- use no more than the following doses (88% of the standard maximum dose):
  - 12 years and older: 16 mg/day
  - younger than 12 years: 0.06 mg/kg per day to a maximum of 2 mg/day

Literature:

Date 13-09-2021

CYP2D6 PM: pimozide

The risk of QT-prolongation - and thereby also the risk of torsade de points - is theoretically increased, because the genetic variation results in an increase in the plasma concentration of pimozide. The elevated plasma concentration and associated theoretical increased risk of QT elongation can be negated by following the dose recommendations provided below.

- use no more than the following doses (58% of the standard maximum dose):
  - 12 years and older: 16 mg/day
  - younger than 12 years: 0.05 mg/kg per day to a maximum of 2 mg/day

Literature:
4. Pharmacogenetic changes to the FDA-approved Orap (pimozide) label include adult and pediatric dosing recommendations for CYP2D6 poor metabolizers. FDA-nieuwsbericht 27-09-11.
5. SmPC Orap (NL en VS).

Date 13-09-2021

CYP2D6 UM: pimozide

NO action is required for this gene-drug interaction.

This gene variation can result in lower pimozide concentrations. However, there is no evidence of reduced effectiveness.

Literature:

Date 13-09-2021

CYP2C19 IM: prasugrel

This is NOT a gene-drug interaction.

Literature:
7. SPC Effient (NL en VS).
CYP2C19 PM: prasugrel

This is NOT a gene-drug interaction.

Literature:

8. SPC Efient (NL en VS).

CYP2C19 UM: prasugrel

This is NOT a gene-drug interaction.

Literature:

2. SPC Efient (NL en VS).

CYP2D6 IM: propafenon

Genetic variation increases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This may increase the risk of side effects.

Recommendation:

Either guide the dose by therapeutic drug monitoring, perform an ECG and be alert to side effects
2. Or choose an alternative Antiarrhythmic drugs that are hardly if at all metabolised by CYP2D6 include, for example, sotalol, disopyramide, quinidine and amioidarone.

Literature:


CYP2D6 PM: propafenon

Genetic variation increases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This increases the risk of side effects.

Recommendation:

1. Reduce the dose to 30% of the standard dose, perform an ECG and monitor plasma concentrations

Literature:

11. SPC Rythmol SR (VS).
CYP2D6 UM: propafenon

Genetic variation decreases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This increases the risk of reduced or no efficacy.

Recommendation:
It is not possible to offer adequately substantiated recommendations for dose adjustment based on the literature.

1. Either monitor plasma concentrations, perform an ECG and be alert to reduced efficacy of the therapy.
2. Or choose an alternative
   Antiarhythmic drugs that are hardly if at all metabolised by CYP2D6 include, for example, sotalol, disopyramide, quinidine and amiodarone.

Literature:

CYP2D6 IM: quetiapine

This is NOT a gene-drug interaction.

Literature:

CYP2D6 PM: quetiapine

This is NOT a gene-drug interaction.

Literature:

CYP2D6 UM: quetiapine

This is NOT a gene-drug interaction.

Literature:
2. Khazaal Y et al. Use of high doses of quetiapine in bipolar disorder episodes are not linked to high activity of cytochrome P450 3A4 and/or cytochrome P4502D6. Psychiatr Q 2013;84:329-35.

CYP3A4 IM: quetiapine

NO action is needed for this gene-drug interaction.

This gene variation reduces the conversion of quetiapine to inactive metabolites and a metabolite with anti-depressant effect. However, the effect on the plasma concentration of quetiapine is limited (20% increase) and it is not known whether this has any clinical consequences. The relationship between the plasma concentration and clinical effect is weak for quetiapine.

Literature:
CYP3A4 PM: quetiapine
The higher plasma concentration of quetiapine is 3.2-fold higher in these patients. In addition, the formation of the active metabolite N-desalkylnquetiapine, which is probably responsible for the antidepressant effect, should be reduced. The gene variation results in reduced activity of the enzyme CYP3A4, which converts quetiapine to N-desalkylnquetiapine and an inactive metabolite.

- indication DEPRESSION - choose an alternative Aripiprazole appears to be less dependent on CYP3A4 for metabolism. Olanzapine is not metabolised by CYP3A4.
- OTHER INDICATIONS - use 38% of the standard dose

NO action is required for this gene-drug interaction.

The higher plasma concentration of quetiapine does not result in an increase in side effects.

Literature:

Date 13-09-2021

CYP2C19 IM: rabeprazole
NO action is required for this gene-drug interaction.

The higher plasma concentration of rabeprazole does not result in an increase in side effects.

Literature:
9. Ariizumi K et al. Therapeutic effects of 10 mg/day rabeprazole administration on reflux esophagitis was not influenced by the CYP2C19 polymorphism. J Gastroenterol Hepatol 2006;21:1428-34.
25. SPC Pariet.

Date 05-03-2018

CYP2C19 PM: rabeprazole
NO action is required for this gene-drug interaction.

The higher plasma concentration of rabeprazole does not result in an increase in side effects.

Literature:
There is currently insufficient information about this gene variation to recommend any action. Moreover, the fact that there are no differences in effectiveness between PM or NO action is required for this gene-drug interaction.
The percentage of patients with therapy failure increased from 16% to 26%. The gene variation increases the plasma concentration of risperidone plus the active metabolite.

There is little evidence to support an increase in side effects caused by the gene variation. The gene variation may lead to a decrease in the required maintenance dose. However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.

Literature:
1. GaoNZ Li et al. ABCB1, ABCG2 and CYP2D6 polymorphism effects on disposition and response to long-acting risperidone. Prog Neuropsychopharmacol Biol Psychiatry 2021;184:110002.

Date 13-09-2015

CYP2D6 IM: risperidone

NO action is needed for this gene-drug interaction.

The percentage of patients with therapy failure increased from 16% to 26%. The gene variation increases the plasma concentration of risperidone plus the active metabolite and increases the proportion of risperidone in this ratio, which is more effective at crossing the blood-brain barrier.

- use 67% of the standard dose
- if problematic side effects originating in the central nervous system occur despite this reduced dose, then reduce the dose further to 50% of the standard dose

Literature:
1. GaoNZ Li et al. ABCB1, ABCG2 and CYP2D6 polymorphism effects on disposition and response to long-acting risperidone. Prog Neuropsychopharmacol Biol Psychiatry 2021;184:110002.
The gene variation has a minor effect on the sertraline plasma concentration. No effect on side effects was found.

**Literature:**


The risk of side effects is increased. The gene variation leads to increased plasma concentrations of sertraline.

- Do not give doses exceeding 75 mg/day
- Guide the dose by response and side effects and/or sertraline plasma concentration.
7. SPC Zoloft.

Date 14-05-2018

CYP2C19 UM: sertraline

NO action is needed for this gene-drug interaction.

The gene variation has a negligible effect on the plasma concentration of sertraline. Moreover, no significant effect on response and side effects has been found.

Date 14-05-2018

CYP2D6 IM: sertraline

This is NOT a gene-drug interaction.

Date 14-05-2018

CYP2D6 PM: sertraline

This is NOT a gene-drug interaction.

Date 14-05-2018

CYP2D6 UM: sertraline

This is NOT a gene-drug interaction.

SLCO1B1 521CC: simvastatin

When using simvastatin 80 mg/day, the risk of myopathy is increased 30-fold to 18% and the risk of severe myopathy is increased 48-fold to 12%. When using 40 mg/day, this risk is increased 7-fold to 1% and 11-fold to 0.68% respectively. The gene variation leads to reduced simvastatin transport to the liver, which increases the simvastatin plasma concentration and therefore the risk of side effects.

1. Choose an alternative
2. Consider any additional risk factors for statin-induced myopathy.
3. Atorvastatin is affected less severely by the SLCO1B1 gene variation, but is also affected by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Use of
atorvastatin is not recommended for patients with additional risk factors for statin-induced myopathy. Rosuvastatin and pravastatin are influenced to a lesser extent by the SLCO1B1 gene variation. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not significantly influenced by the SLCO1B1 gene variation or CYP3A4 inhibitors.

Literature:
8. de Keyser CE et al. The SLCO1B1 c.521T>C polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. Pharmacogenet Genomics 2014;24:43-51.
20. SmPC Zocor.

Date 18-05-2020

SLCO1B1 521TC: simvastatin

When using simvastatin 80 mg/day, the risk of myopathy is increased 5-fold to 3% for moderately severe to severe myopathy and 1.3% for severe myopathy. When using 40 mg/day, this risk is increased 2.6-fold to 0.39% and 0.17% respectively. The gene variation may lead to reduced simvastatin transport to the liver, which may increase simvastatin plasma concentrations and therefore the risk of side effects.

1. Choose an alternative
   Consider any additional risk factors for statin-induced myopathy.
   Atorvastatin is affected less severely by the SLCO1B1 gene variation, but is also affected by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Use of atorvastatin is not recommended for risk factors for statin-induced myopathy.
   Rosuvastatin and pravastatin are influenced to a lesser extent by the SLCO1B1 gene variation. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.
   Fluvastatin is not significantly influenced by the SLCO1B1 gene variation or CYP3A4 inhibitors.

2. If an alternative is not an option:
   1. Avoid simvastatin doses exceeding 40 mg/day
   2. Advise the patient to contact their doctor in the event of muscle symptoms.

Literature:
8. de Keyser CE et al. The SLCO1B1 c.521T>C polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. Pharmacogenet Genomics 2014;24:43-51.
20. SmPC Zocor.
CYP2C9 IM ANDERS: siponimod

Theoretically, the risk of adverse effects in increased, as the genetic variation results in higher plasma concentrations of siponimod.

- use 50% of the normal maintenance dose
- reconsider the choice and the potential benefit of siponimod if the patient is also using a moderate CYP3A4 inducer, such as modafinil

For the comparable genetic variation *1/*3, the moderate CYP3A4 inducer results in a reduction in the exposure of siponimod by 49%, according to a pharmacokinetic model.

Literature:
2. SmPC Mayzent (NL en VS).

CYP2C9 PM ANDERS: siponimod

Siponimod is contraindicated in patients with the comparable genetic variation *3/*3. Theoretically, the risk of adverse effects is greatly increased, as the genetic variation results in much higher plasma concentrations of siponimod.

- avoid siponimod

Literature:
2. SmPC Mayzent (NL en VS).

CYP2C9*1/*2: siponimod

NO action is required for this gene-drug interaction.

The genetic variation can slightly increase the exposure to siponimod. However, the effect is too small to expect any impact on efficacy or adverse effects.

Literature:
2. SmPC Mayzent (NL en VS).

CYP2C9*1/*3: siponimod

Theoretically, the risk of adverse effects in increased, as the genetic variation results in higher plasma concentrations of siponimod.

- use 50% of the normal maintenance dose
- reconsider the choice and the potential benefit of siponimod if the patient is also using a moderate CYP3A4 inducer, such as modafinil

For this genetic variation, a moderate CYP3A4 inducer results in a reduction in the exposure of siponimod by 49%, according to a pharmacokinetic model.

Literature:
2. SmPC Mayzent (NL en VS).

CYP2C9*2/*2: siponimod

NO action is required for this gene-drug interaction.

The genetic variation can slightly increase the exposure to siponimod. However, the effect is too small to expect any impact on efficacy or adverse effects.

Literature:
1. SmPC Mayzent (NL en VS).

CYP2C9*2/*3: siponimod
Theoretically, the risk of adverse effects is increased, as the genetic variation results in higher plasma concentrations of siponimod.

- use 50% of the normal maintenance dose
- reconsider the choice and the potential benefit of siponimod if the patient is also using a moderate CYP3A4 inducer, such as modafinil

For this genetic variation, a moderate CYP3A4 inducer results in a reduction in the exposure of siponimod by 49%, according to a pharmacokinetic model.

Literature:
2. SmPC Mayzent (NL en VS).

Date 12-03-2020

**CYP2C9*3/*3: siponimod**

Siponimod is contraindicated in patients with this genetic variation. Theoretically, the risk of adverse effects is greatly increased, as the genetic variation results in much higher plasma concentrations of siponimod.

- avoid siponimod

Literature:
2. SmPC Mayzent (NL en VS).

Date 12-03-2020

**CYP2D6 IM: sotalol**

This is NOT a gene-drug interaction.

Literature:

Date 24-08-2016

**CYP2D6 PM: sotalol**

This is NOT a gene-drug interaction.

Literature:

Date 24-08-2016

**CYP2D6 UM: sotalol**

This is NOT a gene-drug interaction.

Literature:

Date 24-08-2016

**CYP3A5 heterozygote expresser: tacrolimus**

An increase of the initial dose can result in an increased chance of reaching a tacrolimus concentration within the target range before the start of therapeutic drug monitoring. However, there is no direct evidence that this results in improved clinical results. The genetic variation results in increased conversion of tacrolimus to inactive metabolites and therefore in a higher required dose.

- Indications OTHER than liver transplantation:  - Use 1.5 times the initial dose that would yield the desired result in non-expressers

Adjustment of the dose should then be based on therapeutic drug monitoring.
For example: A Dutch study found a median trough concentration for tacrolimus of 14.7 ng/mL after 3 days at an initial dose of 0.15 mg/kg twice daily for 29 kidney transplant patients who were heterozygous expressers. Their target value was 10 - 15 ng/mL.

- LIVER transplantation:

In addition to the patient’s genotype, the metabolism of tacrolimus is also determined by the genotype of the transplanted liver.

- LIVER is also of the genotype HETEROZYGOUS EXPRESSER:
  - Use 1.5 times the normal initial dose

Adjustment of the dose should then be based on therapeutic drug monitoring.

- LIVER has a DIFFERENT genotype:
  - There is insufficient evidence in the literature to support a dose recommendation.
There is insufficient evidence in the literature to support a dose recommendation.

- Use 2.5 times the initial dose that would yield the desired result in non-expressers

Adjustment of the dose should then be based on therapeutic drug monitoring.

For example: One Dutch study found a median trough concentration for tacrolimus after three days of 9.4 ng/mL at an initial dose of 0.15 mg/kg twice daily for homozygous transplant patients. Their target value was 10 - 15 ng/mL.

- LIVER transplantation:

In addition to the patient's genotype, the metabolism of tacrolimus is also determined by the genotype of the transplanted liver.

- LIVER is also of the genotype HOMOZYGOUS EXPRESSER:

Use 2.5 times the normal initial dose

Adjustment of the dose should then be based on therapeutic drug monitoring.

- LIVER has a DIFFERENT genotype:

There is insufficient evidence in the literature to support a dose recommendation.

Literature:


Date 03-02-2020

CYP3A5 homozygote expresser: tacrolimus

An increase of the initial dose can result in a decreased chance of reaching a tacrolimus concentration within the target range before the start of therapeutic drug monitoring. However, there is no direct evidence that this results in improved clinical results. The genetic variation results in an increased conversion of tacrolimus to inactive metabolites and therefore a higher required dose.

- Indications other than liver transplantation:

- Use 2.5 times the initial dose that would yield the desired result in non-expressers

- LIVER transplantation:

In addition to the patient's genotype, the metabolism of tacrolimus is also determined by the genotype of the transplanted liver.

- LIVER is also of the genotype HOMOZYGOUS EXPRESSER:

Use 2.5 times the normal initial dose

- LIVER has a DIFFERENT genotype:

There is insufficient evidence in the literature to support a dose recommendation.

Literature:

CYP2D6 IM: tamoxifen

This gene variant reduces the conversion of tamoxifen to the active metabolite endoxifen. This results in reduced effectiveness.

Recommendation:
1. select an alternative or measure the endoxifen concentration and increase the dose if necessary by a factor of 1.5-2
2. if TAMOXIFEN is selected: avoid co-medication with CYP2D6 inhibitors such as paroxetine and fluoxetine

Literature:

CYP2D6 PM: tamoxifen

This gene variation reduces the conversion of tamoxifen to the active metabolite endoxifen. This can result in reduced effectiveness.

Recommendation:
1. select an alternative or increase the dose to 40 mg/day and monitor the endoxifen concentration. Studies have demonstrated that PM can achieve an adequate endoxifen concentration when the dose is increased to 40-60 mg/day. Aromatase inhibitors are a possible alternative for post-menopausal women.

Literature:
- SPC Tamoxifen PCH.

Date 09-11-2015

CYP2D6 UM: tamoxifen

NO action is needed for this gene-drug interaction.

As a result of the genetic variation, the plasma concentration of the active metabolites 4-hydroxytamoxifen and endoxifen can increase. However, there is no evidence that this results in an increase in the side effects.

Literature:

Date 09-11-2015

DPD AS 0: tegafur

The gene variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur to inactive metabolites means that the normal dose is an overdose.

- avoid tegafur
- Fluorouracil and capecitabine are not suitable alternatives, as these are also metabolised by DPD.
- If it is not possible to avoid tegafur: start with a very low dose and adjust the initial dose based on toxicity and efficacy. A substantiated recommendation for dose reduction cannot be made based on the literature. The recommendation for fluorouracil and capecitabine is to determine the residual DPD activity in mononuclear cells from peripheral blood and to adjust the initial dose accordingly. A patient with 0.5% of the normal DPD activity tolerated 0.8% of the standard capecitabine dose (150 mg every 5 days). A patient with undetectable DPD activity tolerated 0.43% of the standard capecitabine dose (150 mg every 5 days with every third dose skipped)

Literature:
The gene variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur into inactive metabolites means that the normal dose is an overdose.

- Avoid tegafur or start with a low dose and adjust the initial dose based on toxicity and efficacy
- Fluorouracil and capecitabine are not alternatives, as these are also metabolised by DPD.

For fluorouracil and capecitabine, starting with 50% of the standard dose is recommended and the dose should then be adjusted based on toxicity and effectiveness. In one study, the average dose of fluorouracil/capecitabine after titration was 64% of the standard dose for 17 patients with genotype *1/2846T and 74% of the standard dose for 51 patients with genotype *1/1236A.

Avoid tegafur or start with a low dose and adjust the initial dose based on toxicity and efficacy. Fluorouracil and capecitabine are not alternatives, as these are also metabolised by DPD. It is not possible to offer substantiated advice for dose reduction based on the literature.

Fluorouracil and capecitabine are not alternatives, as these are also metabolised by DPD. It is not possible to offer substantiated advice for dose reduction based on the literature.

For fluorouracil and capecitabine, starting with 50% of the standard dose is recommended.

Literature:
3. SPC Teysuno.

The gene variation increases the risk of severe, possibly fatal toxicity. A reduced conversion of tegafur into inactive metabolites means that the normal dose is an overdose.

- Avoid tegafur or start with a low dose and adjust the initial dose based on toxicity and efficacy
- Fluorouracil and capecitabine are not alternatives, as these are also metabolised by DPD.

For fluorouracil and capecitabine, it is recommended to determine the residual DPD activity in mononuclear cells from peripheral blood and adjust the initial dose based on phenotype and genotype.

Literature:
3. SPC Teysuno.

This is NOT a gene-drug interaction.

Literature:
5. SPC's Brilique (NL) en Brilinta (VS).
CYP2C19: ticagrelor
This is NOT a gene-drug interaction.

Literature:

CYP2C19 UM: ticagrelor
This is NOT a gene-drug interaction.

Literature:

NUDT15: tioguanine
Grade ≥ 2 leukopaenia occurs in an estimated 40% of these patients with standard therapy. The genetic variation increases the concentration of the fully activated metabolite of tioguanine.

- IMMUNOSUPPRESSION:
  - start with 75% of the standard dose
  - Adjustment of the initial dose should be performed based on toxicity (monitoring of the blood counts) and efficacy.
- LEUKAEMIA:
  - start with 75% of the standard tioguanine dose or start with the standard dose and reduce to 75% if side effects necessitate a dose reduction
  - It is not known whether dose reduction in advance results in the same efficacy as dose reduction based on toxicity.
  - Adjustment of the initial dose should be performed based on toxicity (monitoring of the blood counts) and efficacy.

Note: more stringent dose reductions are necessary if the patient is also TPMT IM.

Literature:
13. SmPC Lanvis.
Grade ≥ 2 leukaemia occurs in an estimated 95% of these patients with standard therapy. The genetic variation increases the concentration of the fully activated metabolite of thioguanine.

- Avoid thioguanine
- If it is not possible to avoid thioguanine: use 10% of the standard dose and advise patients to seek medical attention when symptoms of myelosuppression (such as severe sore throat in combination with fever, regular nosebleeds and tendency to bruising) occur.

Any adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and efficacy.

Monitoring should be performed at an increased frequency.

**NOTE:** The percentage of 10% is based on the analogy with azathioprine and mercaptopurine and the analogy with TPMT, for which the gene variants have a comparable effect on toxicity to those of NUDT15. For NUDT15 PM, a percentage of < 20% was calculated for azathioprine and mercaptopurine, but there were insufficient data available to calculate the exact percentage.

**NOTE:** Dose adjustment based on the total of 6-TGN metabolites is not possible for these patients, as they develop toxicity within the therapeutic range that applies for patients without gene variants.

**Literature:**

12. SmPC's Lanvis.

**Date:** 04-03-2019

**TPMT IM: thioguanine**

The risk of serious adverse events such as myelosuppression is increased. The genetic variation increases the concentration of the active metabolites of thioguanine.

- **IMMUNOSUPPRESSION:**
  - Start with 75% of the standard dose
  - Adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and efficacy.

- **LEUKAEMIA:**
  - start with 75% of the standard thioguanine dose, or start with the standard dose and reduce to 75% if side effects necessitate a dose reduction
  - It is not known whether dose reduction in advance results in the same efficacy as dose reduction based on toxicity.
  - The initial dose should be adjusted based on toxicity (monitoring of the blood counts) and efficacy.

**Note:** more stringent dose reductions are necessary if the patient is also NUDT15 IM or NUDT15 PM.

**Literature:**


**Date:** 04-11-2019

**TPMT PM: thioguanine**

The risk of serious, life-threatening adverse events such as myelosuppression is strongly increased. The genetic variation increases the concentration of the active metabolites of thioguanine.

- Choose an alternative or use 6-7% of the standard dose
- Any adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness.
  - If the dose is decreased: advise patients to seek medical attention when symptoms of myelosuppression (such as severe sore throat in combination with fever, regular nosebleeds and tendency to bruising) develop.

**Literature:**

6. SmPC's Lanvis (NL) and Tabloid (VS).
CYP2C9 IM ANDERS: tolbutamide

NO action is required for this gene-drug interaction.

There is insufficient evidence to state that the increased tolbutamide plasma concentration has any clinical consequences.

Literature:

CYP2C9 PM ANDERS: tolbutamide

NO action is required for this gene-drug interaction.

No clinical consequences of the increased tolbutamide plasma concentration were observed.

Literature:

CYP2C9*1/*2: tolbutamide

NO action is required for this gene-drug interaction.

No clinical consequences of the increased tolbutamide plasma concentration were observed.

Literature:

CYP2C9*1/*3: tolbutamide

NO action is required for this gene-drug interaction.

There is insufficient evidence to state that the increased tolbutamide plasma concentration has any clinical consequences.

Literature:
CYP2C9*2/*2: tolbutamide

NO action is required for this gene-drug interaction.

No clinical consequences of the increased tolbutamide plasma concentration were observed.

Literature:

CYP2C9*2/*3: tolbutamide

NO action is required for this gene-drug interaction.

No clinical consequences of the increased tolbutamide plasma concentration were observed.

Literature:

CYP2D6 IM: tramadol

The genetic variation reduces the conversion of tramadol to a metabolite with a higher activity. This can result in reduced analgesia.

Recommendation:
It is not possible to provide a specific recommendation for dose adjustment, because the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes.

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
   1. try a dose increase
   2. if this does not work: choose an alternative
      Do not select codeine, as this is also metabolised by CYP2D6.
      Morphine is not metabolised by CYP2D6.
5. if no alternative is selected: advise the patient to report inadequate analgesia

Literature:
6. Kim E et al. Adverse events in analgesic treatment with tramadol associated with CYP2D6 extensive-metaboliser and OPRM1 high-expression variants. Ann Rheum Dis
CYP2D6 PM: tramadol

The genetic variation reduces the conversion of tramadol to a metabolite with a higher activity. This can result in reduced analgesia.

Recommendation:
It is not possible to provide a specific recommendation for dose adjustment, because the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes.

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
   1. try a dose increase.
   2. if this does not work: choose an alternative
      Do not select codeine, as this is also metabolised by CYP2D6.
      Morphine is not metabolised by CYP2D6.
   Oxycodeone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
3. if no alternative is selected: advise the patient to report inadequate analgesia

Literature:

CYP2D6 UM: tramadol

The genetic variation increases the conversion of tramadol to a metabolite with a stronger opioid effect. This can result in an increase in potentially life-threatening side effects.

Recommendation:
As the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes, the effect of a dose reduction cannot be predicted with certainty.

- select an alternative
  Do not choose codeine, as it is contra-indicated for CYP2D6 UM.
  Morphine is not metabolised by CYP2D6.
  Oxycodeone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.
- if an alternative is not possible:
  - dose increase of the standard dose
  - advise the patient to report side effects (such as drowsiness, confusion, constipation, nausea and vomiting, respiratory depression or urine retention).

Literature:
10. SPC Ultram (VS).

CYP2D6 IM: venlafaxine

There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.

Literature:


- avoid venlafaxine
- Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline.

if it is not possible to avoid venlafaxine and side effects occur:
1. reduce the dose
2. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine

It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.

**CYP2D6 PM: venlafaxine**

There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.

It is not possible to offer adequately substantiated advice for dose reduction based on the literature.

- avoid venlafaxine
- Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline.

if it is not possible to avoid venlafaxine and side effects occur:
1. reduce the dose
2. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine

It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.

**CYP2D6 UM: venlafaxine**

It may be difficult to adjust the dose for patients due to altered metabolism between venlafaxine and the active metabolite O-desmethylvenlafaxine. The gene variation increases the conversion of venlafaxine to O-desmethylvenlafaxine and reduces the sum of venlafaxine plus O-desmethylvenlafaxine.

1. be alert to a possible decrease in the sum of the plasma concentrations of venlafaxine and the active metabolite O-desmethylvenlafaxine
2. if necessary, increase the dose to 150% of the standard dose
3. dose adjustment does not result in efficacy without unacceptable side effects or if dose adjustment based on therapeutic drug monitoring is not possible, then venlafaxine should be avoided

Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline.
Recommendation:

Initially, the risk of side effects is of particular interest. The gene variation can reduce the conversion of voriconazole and consequently increase the plasma concentration. This could result in improved efficacy or an increase in the risk of side effects.

Recommendation:

- Monitor the plasma concentration

Literature:

25. SPC Vfend.

Date 01-03-2019

CYP2C19 IM: voriconazol

The gene variation can reduce the conversion of voriconazole and consequently increase the plasma concentration. This could result in improved efficacy or an increase in the risk of side effects.

Recommendation:

- Use 50% of the standard dose and monitor the plasma concentration

Literature:


Date 01-05-2017

CYP2C19 PM: voriconazol

The gene variation can reduce the conversion of voriconazole and consequently increase the plasma concentration. This could result in improved efficacy or an increase in the risk of side effects.

Initially, the risk of side effects is of particular interest.

Recommendation:

- Use 50% of the standard dose and monitor the plasma concentration

Literature:

22. SCC Vred.

Date 01-05-2017

CYP2C19 UM: voriconazole

The gene variation increases the conversion of voriconazole, which increases the risk of ineffectiveness.

Recommendation:

- Use an initial dose that is 1.5x higher and monitor the plasma concentration

Literature:


Date 01-05-2017

CYP2C9 IM ANDERS: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

- Use 65% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm. Algorithms for Caucasian patients usually contain only the *2 and *3 allele. If the activity of the reduced-activity alleles is comparable to the activity of *2 or *3, then the algorithm can be completed as if *2 or *3 is present. See https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics for Excel files containing calculation modules for oral and equivalent intravenous doses. From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Literature:

9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9 PM ANDERS: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

- Use 20% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm. Algorithms for Caucasian patients usually contain only the *2 and *3 allele. If the activity of the reduced-activity alleles is comparable to the activity of *2 or *3, then the algorithm can be completed as if *2 or *3 is present. See https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics for Excel files containing calculation modules for oral and equivalent intravenous doses. From day 6 on the standard algorithm without genotype information can be used to calculate the dose.
Modified dose algorithms have been developed for patients of African or (East) Asian heritage.

Literature:

9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9*1/*2: warfarine

NO action is required for this gene-drug interaction.

Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this causes problems when therapy is initiated as usual.

Date 24-08-2016

CYP2C9*1/*3: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

1. use 65% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see https://www.knmp.nl/producten-ondernemen/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics.

From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Date 24-08-2016

CYP2C9*2/*2: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

1. use 65% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see https://www.knmp.nl/producten-ondernemen/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics.

From day 6 on the standard algorithm without genotype information can be used to calculate the dose.
Literature:

9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9*2/*3: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

1. use 45% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics.

From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Date 24-08-2016

CYP2C9*3/*3: warfarine

This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.

Recommendation:

1. use 20% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics.

From day 6 on the standard algorithm without genotype information can be used to calculate the dose.

Date 24-08-2016

VKORC1 -1639 AA: warfarine

The genetic variation results in increased sensitivity to warfarin. This results in an increase in the risk of excessively severe inhibition of blood clotting (INR > 4) during the first month of the treatment.

Recommendation:

1. use 60% of the standard initial dose

The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT: see https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica.

From day 6 on the standard algorithm without genotype information can be used to calculate the dose.
Literature:

10. SmPC Coumadin (VS).

Date 24-08-2016

**VKORC1 -1639 GA: warfarine**

NO action is required for this gene-drug interaction.

The genetic variation results in a reduction in the required dose and an increase in the risk of excessively severe inhibition of blood clotting during the first month of the treatment. However, the effect is small and GA is also the most common genotype, meaning that the standard treatment will primarily be based on patients with this genotype.

Literature:

9. SmPC Coumadin (VS).

Date 24-08-2016

**CYP2D6 IM: zuclopentixol**

The risk of side effects may be elevated. The genetic variation leads to decreased conversion of zuclopentixol, which causes the plasma concentration to be approximately 1.35-fold higher.

- use 75% of the standard dose

Literature:

7. SmPC’s Cisordinol en Cisordinol Depot.

Date 13-09-2021

**CYP2D6 PM: zuclopentixol**

The risk of side effects may be elevated. The genetic variation results in a decreased conversion of zuclopentixol, which causes the plasma concentration to be approximately 1.6-fold higher.

- use 50% of the standard dose

Literature:

8. SmPC’s Cisordinol en Cisordinol Depot.
CYP2D6 UM: zuclopentixol

The risk of ineffectiveness may be elevated. The genetic variation leads to an increased conversion of zuclopentixol, which can result in a reduction of the plasma concentration.

There is insufficient information available to make a dosage recommendation. - if the effectiveness is insufficient: try a dose increase Do not exceed 1.5 times the standard dose

Literature:


3. SmPC's Cisordinol en Cisordinol Depot.