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:


17. SmPC Ziegens (NL en VS).

CYP2C9 IM 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 13-05-2015

CYP2C9 IM ANDERS: acenocoumarol

1868
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:


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:


Markatos CN et al. VKORC1 and CYP2C9 allelic variants influence acenocoumarol dose requirements in Greek patients. Pharmacogenomics 2008;9:1631-8.


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.

CYP2C9*1/*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).

**Literature:**


**CYP2C9*2/*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:**

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 usual (i.e. with frequent INR monitoring).

Date 14-05-2018

**CYP2C9*2/*3: acenocoumarol**

### Literature


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 usual (i.e. with frequent INR monitoring).
CYP2C9*3/-4: 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:


CYP2C9*3/-4: 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.knmp.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.


Literature:

that a stronger inhibition of the uric acid production by allopurinol is required to achieve the desired uric acid concentration. 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

**VKORC1 -1639 GA: alacenocoumarol**

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: allopenrinol**

The effectiveness of allopenrinol 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 allopenrinol 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:**

4. Montes R et al. ABC2G 141KK: allopenrinol

**ABC2G 141OQ: allopenrinol**

The effectiveness of allopenrinol 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 allopenrinol 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**

**ABC2G 141OQ: allopenrinol**

The effectiveness of allopenrinol 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 allopenrinol 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:**

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.
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 Aposet.

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 nortriptiline 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 nortriptiline 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 nortriptiline 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 nortriptiline 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.

CYP2D6 IM: aripiprazol

NO action is needed for this gene-drug interaction.

The genetic variation increases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is insufficient evidence that this increases the risk of side effects.

- use information for drug-drug interaction.
CYP2D6 PM: aripiprazol

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).

Literature:

9. SmPC’s Abilify (NL), Abilify Maintena (NL), Abilify (USA) en Aristad (USA).

CYP2D6 UM: aripiprazol

NO action is needed for this gene-drug interaction.

The genetic variation decreases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is no evidence that this increases the risk of reduced effectiveness.

Literature:


CYP2D6 IM: atenolol

This is NOT a gene-drug interaction.

Literature:


CYP2D6 PM: atenolol

This is NOT a gene-drug interaction.

Literature:

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.

As a result, the plasma concentration of the active ingredients decreases. If the medicine is effective, but side effects occur: reduce the dose and check whether the effect is conserved.

The plasma concentration of atorvastatin is a factor of 2-3 times higher for IM than for NM at the same dose.

CYP2D6 IM: atomoxetine

The dose requirement can be reduced, because the genetic variation results in a higher atomoxetine plasma concentration.

- in the event of side effects occurring and/or a response later than 9 weeks: reduce the dose and check whether the effect is conserved.
- The plasma concentration of atomoxetine is a factor of 8-11 times higher for PM than for NM at the same dose.

CYP2D6 PM: atomoxetine

The risk of side effects is increased, because the genetic variation results in a higher atomoxetine plasma concentration.

- start with the normal initial dose, bearing in mind that an increase in this dose probably will not be required.
- advise the patient to report side effects (such as decreased appetite, vomiting, abdominal pain, constipation, insomnia, early waking, drowsiness, irritability, pupil dilation and itching).
- if the medicine is effective, but side effects occur: reduce the dose and check whether the effect is conserved.
- The plasma concentration of atomoxetine is a factor of 2-3 times higher for PM than for NM at the same dose.

CYP2D6 UM: atomoxetine

Efficacy can be reduced due to the gene variation. The gene variation results in an increased conversion of atomoxetine to the active metabolite 4-hydroxyatomoxetine, which has a much lower plasma concentration.

As a result, the plasma concentration of the active ingredients decreases.

- be extra alert to reduced efficacy of the treatment.
- advise the patient to report an inadequate effect.
- an alternative can be selected as a precaution.

Clonidine is not metabolised by CYP2D6.

Literature:

Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy:

1. Choose an alternative

2. If no 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.

Literature:


Date 18-05-2020

SLCO1B1 521TC: atorvastatin

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

1. Choose an alternative

2. If no 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.

Literature:

NUDT15 IM: azathioprine/mercaptopurine

Grade ≥ 2 leukaemia occurs in 42% of these patients with standard immunosuppression therapy. The gene variation increases the concentration of the fully activated metabolite of azathioprine and mercaptopurine.

- **IMMUNOSUPPRESSION:**
  - start with 50% of the standard dose
  - 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.

- **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
  - 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: 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.

Literature:

12. SmPC’s Puri-Nethol es Imuran.

NUDT15 PM: azathioprine/mercaptopurine

Grade ≥ 2 leukaemia occurs in 96% of these patients with standard therapy. The gene variation increases the concentration of the fully activated metabolite of azathioprine and mercaptopurine.

- **avoid azathioprine and mercaptopurine**
- **if it is not possible to avoid azathioprine and mercaptopurine: 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 adjust of the initial dose should be guided by toxicity (monitoring of blood counts) and efficacy.

Note: The percentage of 10% 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.

Literature:

5. SmPC’s Puri-Nethol es Imuran.
Grade ≥ 2 leukopenia occurs in 23% of these patients with normal therapy for immunosuppression. The genetic variation increases the quantity of the active metabolites of azathioprine and mercaptopurine.

 Recommendation:

- **IMMUNOSUPPRESSION**
  - Start with 50% of the standard dose
  - Adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness.
  - Dose adjustment is not required for doses lower than 1.5 mg/kg per day for azathioprine or 0.75 mg/kg per day for mercaptopurine.

- **LEUKAEMIA**
  - Start with 50% of the standard mercaptopurine dose, or start with the standard dose and reduce to 50% 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:

6. Lenard L et al. Thiouracil dose intensity and treatment outcome in childhood lymphoblastic leukaemia: the influence of thiouracil methyltransferase pharmacogenetics, SmPC’s Imuran (NL) en VS), Puri-Nethol (NL) en Purixan (VS).
17. SmPC’s Imuran (NL en VS), Purixan (NL) en Purixan (VS).

Date 17-09-2019

**CYP2D6 IM: bisoprolol**

This is NOT a gene-drug interaction.

**Literature:**

Date 12-09-2022

**CYP2D6 PM: bisoprolol**

This is NOT a gene-drug interaction.

**Literature:**

Date 12-09-2022

**CYP2D6 UM: bisoprolol**

This is NOT a gene-drug interaction.

**Literature:**
**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 PM: 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 UM: 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:
7. SmPC’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
Phenytoin, 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:
The plasma concentration of carvedilol can be reduced. This does not, however, result in a decrease in the effectiveness.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.
**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:**

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**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:**

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**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:**

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**Date 12-09-2022**

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**Date 14-05-2018**

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**Date 14-05-2018**
CYP2D6 IM: citalopram/escitalopram

This is NOT a gene-drug interaction.

Literature:
10. SPC Cipramil.

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 does increase 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:

Date 04-03-2019

CYP2C19 UM: clomipramine

The gene variation increases the risk of ineffective treatment for obsessive compulsive disorder and anxiety disorders by reducing the plasma concentration of clomipramine. The gene variation has no impact 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.
  - Monitor the effect and side effects or the plasma concentrations of clomipramine and desmethylclomipramine

- For obsessive compulsive disorder, the therapeutic plasma concentration of clomipramine is greater than 200 ng/mL in combination with a plasma concentration of desmethylclomipramine that is as low as possible.
- 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.
- A sum of the plasma concentrations of clomipramine and desmethylclomipramine exceeding 600 ng/mL is considered toxic.
- Add a low dose of fluvoxamine if necessary, to inhibit CYP2C19 and CYP1A2 and thereby inhibit the conversion of clomipramine to desmethylclomipramine

- **Indication DEPRESSION:**
  - No action required

Literature:

Date 04-03-2019

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:

Date 19-11-2018

CYP2D6 PM: 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.

- **Indication DEPRESSION:**
  - Use 50% of the standard dose and monitor the effect and side effects or the plasma concentrations of clomipramine and desmethylclomipramine in order to set the maintenance dose.

  - The therapeutic range is 200-400 ng/mL for the sum of the plasma concentrations of clomipramine and desmethylclomipramine. Values higher than 600 ng/mL are considered toxic.

- **Indication ANXIETY DISORDERS or OBSESSIVE COMPULSIVE DISORDER:**
  - If side effects occur: use 50% of the standard dose and monitor the effect and side effects or the plasma concentrations of clomipramine and desmethylclomipramine in order to set the maintenance dose.

  - 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 retained. Clomipramine and desmethylclomipramine both contribute to the side effects. Only clomipramine contributes to the effectiveness.

  - 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, 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 cardioxic side effects may be increased. The gene variation leads to reduced plasma concentrations of clomipramine and the active metabolite desmethytlclomipramine and to increased concentrations of the potentially cardioxic hydroxy metabolites.

- use 1.5 times the standard dose and monitor the effect and side effects of the plasma concentrations of clomipramine and desmethylclomipramine 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 desmethylclomipramine.

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

- if a dose increase is not wanted due to potential cardioxic 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 31-01-2022

CYP2D6 PM: clonidine

This is NOT a gene-drug interaction.

Literature:

Date 31-01-2022

CYP2D6 UM: clonidine

This is NOT a gene-drug interaction.
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)

- OTHER INDICATIONS:
  - no action required

Literature:

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).

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**Literature:**

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

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**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. Vilkki M et al. CYP1A2 polymorphism -1545C > T (rs2470859) is associated with increased side effects to clozapine. BMC Psychiatry 2014;14:50.

Date 13-09-2021

CYP1A2*1C-heterozygous: clozapine

This is NOT a gene-drug interaction.

Literature:

Date 13-09-2021

CYP1A2*1C: clozapine

This is NOT a gene-drug interaction.

Literature:

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:
Literature:


Date 13-09-2021

CYP2D6 PM: 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:


Date 13-09-2021

CYP2D6 UM: clozapine

NO action is required for this gene-drug interaction.

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

Literature:


12. SmPC Clozaril (VS).

Date 13-09-2021

CYP2D6 IM: codeine

The genetic variation reduces 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. 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.
     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.
  3. if no alternative is selected: advise the patient to report inadequate analgesia.

Literature:
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 Codeinefosfato Ratiopharm.

CYP2D6 PM: codeine

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

 Recommendation:

- For COUGH: 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.
  - 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.
  - If an alternative is not an option, advise the patient to report inadequate analgesia.

Literature:

17. SPC Codeinefosfato Ratiopharm.
CYP2D6 IM: disopyramide
This is NOT a gene-drug interaction.

Literature:
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Date 12-09-2022
CYP2D6 PM: disopyramide
This is NOT a gene-drug interaction.

Literature:
'

Date 12-09-2022
CYP2D6 UM: disopyramide
This is NOT a gene-drug interaction.

Literature:
'

Date 12-09-2022
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

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:
6. SmPC Silenor (VS).

CYP2D6 PM: doxepine

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:
1. Kuzin M et al. The role of the poor metabolizer genotype CYP2D6 and CYP1A2 phenotype in the pharmacokinetics of duloxetine and venlafaxine-a case report. Basic Clin

CYP2D6 UM: doxepine

This is NOT a gene-drug interaction.

Literature:
2. Kuzin M et al. The role of the poor metabolizer genotype CYP2D6 and CYP1A2 phenotype in the pharmacokinetics of duloxetine and venlafaxine-a case report. Basic Clin

CYP2D6 IM: duloxetine

This is NOT a gene-drug interaction.

Literature:
2. Kuzin M et al. The role of the poor metabolizer genotype CYP2D6 and CYP1A2 phenotype in the pharmacokinetics of duloxetine and venlafaxine-a case report. Basic Clin

CYP2D6 PM: duloxetine

This is NOT a gene-drug interaction.

Literature:
1. Kuzin M et al. The role of the poor metabolizer genotype CYP2D6 and CYP1A2 phenotype in the pharmacokinetics of duloxetine and venlafaxine-a case report. Basic Clin
The dosing recommendations above are based on PM patients with the *6/*6 genotype. There is evidence that the *18/*18 genotype in PM patients (only present in ...
negroid patients) may require greater dose reductions.

Considerations:
Detailed justification for the recommendation is contained in the risk analysis. The considerations used for adults are also given below.

The median or mean plasma concentrations or AUC in PM patients are above the therapeutic range, except in 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 of *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
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.
  - 1. choose an alternative if possible
    - Strong CYP2D6 inhibitor: for example paroxetine, fluoxetine, quinidine, bupropione.
    - Moderate CYP2D6 inhibitor: for example duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone. Strong CYP3A inhibitor: for example ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir.
  - Moderate CYP3A inhibitor: for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aripiprazol, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine.

- **Co-medication with a STRONG CYP2D6 INHIBITOR (e.g. paroxetine, fluoxetine, quinidine, bupropione):**
  - 1. use a dose of 84 mg eliglustat 1x daily
  - 2. be alert to side effects

- **Co-medication with a MODERATE CYP2D6 INHIBITOR (for example duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone):**
  - 1. consider a dose of 84 mg eliglustat 1x daily
  - 2. be alert to side effects

- **Co-medication with a STRONG CYP3A INHIBITOR (for example ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir):**
  - be an alternative if possible
  - if an alternative is not an option:
    - consider a dose of 84 mg eliglustat 1x daily
  - 2. be alert to side effects

- **Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aripiprazol, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine):**
  - 1. choose an alternative
  - 2. if an alternative is not an option:
    - consider a dose of 84 mg eliglustat 1x daily
  - 2. be alert to side effects

- **Co-medication with a STRONG CYP3A INDUCER (for example rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutin, 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 moderate or strong CYP2D6 or CYP3A inhibitor or strong CYP3A inducer:**
  - 1. use the standard dose of 84 mg 2x daily

Literature:

1. SVC’s Cerdelga (Nederland en VS).

Date 31-10-2016

CYP3A 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 ketokonazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir):**
  - Eliglustat is contra-indicated.
  - 1. choose an alternative if possible

Date 05-03-2018

CYP2B6 IM: telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir.

Literature:

Literature:

Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aperatint, darunavir, fosaprepitant, imatinib, cinclideine):

1. choose an alternative if possible

Co-medication with a WEAK CYP3A INHIBITOR (for example amlopidine, cilostazole, fluvoxamine, goldenseal, isoniazide, ranitidine, ranolazine):

1. choose an alternative for the weak CYP3A inhibitor if possible
2. if an alternative is not an option:
   1. use a dose of 84 mg eliglustat 1x daily
   2. be alert to side effects

Co-medication with a STRONG CYP3A INDUCER (for example rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutine, hypericum):

Eliglustat is contra-indicated.

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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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,
17. SPC’s Lexapro (NL en VS).

Date 14-05-2018

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:

Date 14-05-2018

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:

Date 05-03-2018
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 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).

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).

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).
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/*2: phenprocoumon

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:

**Date 14-05-2018**

**CYP2C9*2/*3: fenprocoumon**

NO action is required for this gene-drug interaction.

The genetic variation can result in a reduction in the required maintenance dose and possibly in an extension of the time required to achieve a stable INR. 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*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:**

Literature:


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 a ANTICOAGULATION CLINIC: recommend to use 50% of the standard initial dose
- NO monitoring by an 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:


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:


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:
5. Tassaneeyakul W et al. Associations between HLA class I and cytochrome P450 2C9 genetic polymorphisms and phenytoin-related severe cutaneous adverse reactions in a Thai population. Pharmacogenomics 2016;26:225-34.

Date 23-05-2022

CYP2C9*1/*2: fenitoin

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

Literature:

Date 23-05-2022
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:

2. For the other doses, use 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:

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

Literature:

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

Literature:

5. The loading dose does not need to be adjusted.
6. For the other doses, use 50% of the standard dose and assess the dose based on effect and serum concentration after 7-10 days.
7. Advise the patient to get in touch if side effects (such as ataxia, nystagmus, slurred speech, sedation or rash) occur.
**HLA-B*1502: phenytoine**

The life-threatening cutaneous side effect Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) occurs more frequently in patients with this genetic variation. The calculated risk of phenytoin-induced SJS/TEN in patients with HLA-B*1502 is 0.65%.

- carefully weigh the risk of SJS/TEN against the benefits
- avoid phenytoin if an alternative is possible

Carbamazepine carries a 10-fold higher risk of SJS/TEN for these patients and is therefore not an alternative. A comparable risk has been reported for lamotrigine as for phenytoin. The same applies for oxcarbazepine, but the most severe forms (SJS/TEN overlap and TEN) are not observed with oxcarbazepine.
- if it is not possible to avoid this medication, then advise the patient to report any skin rash immediately

**Literature:**

15. SmPC Diphtantoïne-Z.
16. SmPC Dilantin (VSI).

**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:**


**CYP2D6 PM: flecainide**

The genetic variation reduces conversion of flecainide to inactive metabolites. This increases the risk of side effects.

**Recommendation:**

1. reduce the dose to 50% of the standard dose and record an ECG and monitor the plasma concentration

**Literature:**


Date 23-05-2022

Date 12-09-2022

Date 12-09-2022
The genetic variation increases conversion of flecainide to inactive metabolites. A higher dose is possibly required as a result.

Recommendation:

- 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:

1. monitor the patient’s liver function
2. choose an alternative if liver enzymes and/or bilirubin levels are elevated

Examples of anti-arrhythmic drugs that are not metabolised via CYP2D6 (or to a lesser extent) include sotalol, disopyramide, quinidine and amiodarone.

Literature:

6. SmPC Floxapen.

A very low risk of severe 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

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.

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 diarrhoea

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.
**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 fluoruracil dose).

- be alert to the occurrence of severe side effects, such as leukopaenia, neutropaenia, thrombocytopaenia and diarrhoeas.

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 15-11-2021**

**DPD AS 0: fluorouracil cutan**

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 Efudix crème en Carac cream (VS).

**Date 13-05-2019**

**DPD 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.

After starting treatment, the dose should be adjusted based on toxicity and effectiveness. In a study involving 17 patients with genotype 1/2846T, the average dose after titration was 64% of the standard dose. For 51 patients with genotype 1/1236A, the average dose after titration was 74% of the standard dose. Tegafur is not an alternative, as this is also metabolised by DPD.

**Literature:**


Tegafur is not an alternative, as this is also metabolised by DPD.

Adjustment of the subsequent dose should be guided by toxicity and effectiveness. However, in one study involving 17 patients with gene activity 1, the average dose after titration was 57% of the standard dose. Tegafur is not an alternative, as this is also metabolised by DPD.

Literature:


36. 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 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 dose 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.

Tegafur is not an alternative, as this is also metabolised by DPD.

Literature:


15. SPC's Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS) en Xeloda (VS).

Date 13-05-2019

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:


15. SPC's Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS) en Xeloda (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 nortriptyline. Hum Psychopharmacol 2004;19:17-23.
7. SPC Prozac, 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:

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:**


SLCO1B1 521TC: 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:**


CYP2C19 IM: fluvoxamine

This is NOT a gene-drug interaction.

**Literature:**


CYP2C19 PM: fluvoxamine

This is NOT a gene-drug interaction.
Literature:


Date 14-05-2018

CYP2C19 UM: fluvoxamine 3511

This is NOT a gene-drug interaction.

Date 14-05-2018

CYP2D6 IM: fluvoxamine 5994

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 insufficient scientific substantiation of an increase in the risk of side effects.

Date 14-05-2018

CYP2D6 PM: fluvoxamine 5993

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 evidence to substantiate an increase in the risk of adverse events.

Date 14-05-2018

CYP2D6 UM: fluvoxamine 5995

NO action is needed for this gene-drug interaction.

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

Date 14-05-2018

CYP2D6 UM: fluvoxamine 5995

NO action is needed for this gene-drug interaction.

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

Date 14-05-2018

CYP2D6 UM: fluvoxamine 5995

NO action is needed for this gene-drug interaction.

The plasma concentration of fluvoxamine can decrease as a result of the increased activity of CYP2D6. However, there is no scientific substantiation of a reduced effectiveness.
The gene variation has no effect on the treatment with folic acid. Treatment with folic acid decreases the reduction of folate concentrations caused by the gene variation.

### Literature:


Date 07-06-2021

### MTHFR 677T: foliumzuur

NO action is required for this gene-drug interaction.

The gene variation has no effect or a positive effect on the treatment with folic acid. Treatment with folic acid decreases the reduction of folate concentrations caused by the gene variation.

### 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.
**CYP2D6 UM: gefitinib**

4873

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.

**CYP2C9 IM ANDERS: glibenclamide**

1882

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.

**CYP2C9*1/*2: glibenclamide**

1877

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.

**CYP2C9*1/*3: glibenclamide**

1878

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/*3.
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:
**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:**

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

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**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:**

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**CYP2C9*2/*2: gliclazide**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide.

**Literature:**

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**CYP2C9*2/*3: gliclazide**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide.

**Literature:**

Date 20-11-2017

CYP2C9*3/*3: glimepiride
NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of glimepiride without significantly increasing the risk of hypoglycaemia.

Literature:

Date 20-11-2017

CYP2C9 IM ANDERS: glimepiride
NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of glimepiride.

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 ureas derivatives than the occurrence of hypoglycaemia.

Literature:

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.

Literature:
**CYP2C9*1/*3: glimepiride**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of glimepiride.

**Literature:**

**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.

**Literature:**

**Date 20-11-2017**

**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:**

**Date 20-11-2017**

**CYP2C9*3/*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**

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

**Literature:**

5. van der Weide K et al. The influence of the CYP3A4*22 polymorphism and CYP2D6 polymorphisms on serum concentrations of aripiprazole, haloperidol, pimozide, and risperidone in psychiatric patients. J Clin Psychopharmacol 2015;35:228-36 and personal communication (mean dose-corrected trough concentrations).

**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 40% lower.

- use 1.5 times the standard dose or choose an alternative. Antipsychotics that are not metabolised by CYP2D6 - or to a much lesser extent - include, for example, flupentixol, PENfluridol, quetiapine, olanzapine or clozapine.

**Literature:**

2. van der Weide K et al. The influence of the CYP3A4*22 polymorphism and CYP2D6 polymorphisms on serum concentrations of aripiprazole, haloperidol, pimozide, and risperidone in psychiatric patients. J Clin Psychopharmacol 2015;35:228-36 and personal communication (mean dose-corrected trough concentrations).

**CYP2D6 UM: haloperidol**

There are indications of a risk of reduced effectiveness. The genetic variation leads to an increased conversion of haloperidol, resulting in plasma concentration that is approximately 40% lower.

- use 1.5 times the standard dose or choose an alternative. Antipsychotics that are not metabolised by CYP2D6 - or to a much lesser extent - include, for example, flupentixol, PENfluridol, quetiapine, olanzapine or clozapine.

**Literature:**

2. van der Weide K et al. The influence of the CYP3A4*22 polymorphism and CYP2D6 polymorphisms on serum concentrations of aripiprazole, haloperidol, pimozide, and risperidone in psychiatric patients. J Clin Psychopharmacol 2015;35:228-36 and personal communication (mean dose-corrected trough concentrations).

**Date 13-09-2021**
**CYP2C19 IM: imipramine**

NO action is required for this gene-drug interaction.

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

**Literature:**


Date 10-09-2018

**CYP2C19 PM: imipramine**

The risk of side effects is increased. The gene 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:**


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:**

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:


7. SmPC Tofranil-PM (VS).

Date 07-06-2021

CYP2D6 UM: 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 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:


Date 19-11-2018

UGT1A1 IM ANDERS: irinotecan

NO action is needed for this gene-drug interaction.

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.


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.

**UGT1A*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.

**UGT1A1*1/*28 polymorphisms are correlated with irinotecan-induced toxicity: a meta-analysis.** Asia Pac J Clin Oncol 2018;14:479-489.


**Chen X et al. UGT1A1 polymorphisms with irinotecan-induced toxicities and treatment outcome in Asians with lung cancer: a meta-analysis.** Cancer Chemother Pharmacol 2017;79:1109-1117.


**Literature:**

1. Yang Y et al. UGT1A1 and UGT1A128 polymorphisms are correlated with irinotecan-induced toxicity: a meta-analysis. Asia Pac J Clin Oncol 2018;14:479-489.


CYP2D6 IM: kineidine

This is NOT a gene-drug interaction.

Date 07-06-2021

CYP2D6 PM: kineidine

This is NOT a gene-drug interaction.

Date 12-09-2022

CYP2D6 IM: kineidine

This is NOT a gene-drug interaction.

Date 07-06-2021

CYP2D6 PM: kineidine

This is NOT a gene-drug interaction.

Date 12-09-2022
CYP2D6 UM: kinzideine

This is NOT a gene-drug interaction.

Literature:


Date 12-09-2022

HLA-B*1502: lamotrigine

The life-threatening cutaneous side effect Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) occurs more often in patients with this genetic variation. Based on the estimated risk for all patients and the increase by a factor 3.6 for patients with this genetic variation, the risk of lamotrigine-induced SJS/TEN in patients with HLA-B*1502 is estimated at 0.4%.

- carefully weigh the risk of SJS/TEN against the benefits
- avoid lamotrigine if an alternative is available

Carbamazepine carries a much higher risk of SJS/TEN in these patients and is therefore not an alternative.

A similar risk has been reported for phenytoin as for lamotrigine. The same applies to oxcarbazepine, but the most severe forms (SJS/TEN overlap and TEN) have not been observed with oxcarbazepine.

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

Literature:


Date 12-09-2022

CYP2C19 IM: lansoprazol

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:

NO action is needed for this gene-drug interaction.

Date 05-03-2018

CYP2C19 UM: lansoprazol

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

Recommendation:

- For Helicobacter pylori ERADICATION THERAPY:
  1. Use a 4-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 4-fold higher dose
  3. Advise the patient to report persisting symptoms of dyspepsia

Literature:

41. SPC Prezal.

Date 07-06-2021

**MTHFR 677TT: methotrexat**

This is NOT a gene-drug interaction.

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**Literature:**


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**COMT Met/Met: methylfenidaat**

This is NOT a gene-drug interaction.

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**Literature:**


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**Date 07-06-2021**

**COMT Met/Met: methylfenidaat**

This is NOT a gene-drug interaction.

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**Literature:**

COMT Val/Met: methylfenidaat

This is NOT a gene-drug interaction.

Literature:


CYP2D6 IM: methylfenidaat

This is NOT a gene-drug interaction.

Literature:


CYP2D6 PM: methylfenidaat

This is NOT a gene-drug interaction.

Literature:


CYP2D6 UM: methylfenidaat

This is NOT a gene-drug interaction.

Literature:


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

Literature:

**Recommendation:**

was no effect on the blood pressure and hardly any effect on the reduction of the heart rate.

**Literature:**

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

- **OTHER CASES:**
  - 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: no action required.

**Literature:**


**Date 12-09-2022**

**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

**Literature:**

- **CYP2D6 PM: metoprolol**
75. 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 12-09-2022

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

Literature:

Date 14-11-2022

CYP2C19 PM: mirtazapine
This is NOT a gene-drug interaction.

Literature:

Date 14-11-2022

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

Literature:

Date 14-11-2022

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:

Date 14-11-2022

CYP2D6 PM: mirtazapine

2001
NO action is required for this gene-drug interaction.

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

Literature:

Date 14-11-2022

**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:

Date 14-11-2022

**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. SmPC Moclobemide Mylan.

Date 14-11-2022

**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. SmPC Moclobemide Mylan.

Date 14-11-2022

**CYP2C19 UM: moclobemide**

NO action is required for this gene-drug interaction.

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

Literature:
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. SmPC Moclobemide Mylan.

Date 14-11-2022

**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:

Date 19-11-2018

**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 2D6 poor metabolizers treated with fluoxetine or nortriptyline. Hum Psychopharmacol 2004 Jan;19:17-23.
10. SmPC Pamelor (VS).

Date 19-11-2018

**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-hydroxy-nortriptyline.

- 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-hydroxy-nortriptyline.
- Plasma concentrations of Z-hydroxy-nortriptyline 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:

Date 19-11-2018

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**NO action is needed for this gene-drug interaction.**

Plasma concentrations of the cardiotoxic metabolite Z-10-hydroxynortriptyline. 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-hydroxy-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:
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.
14. Czerwensky F et al. CYP1A2*1D and *1F polymorphisms have a significant impact on olanzapine serum concentrations. Ther Drug Monit 2015;37:152-60.
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.
5. Looman NMG et al. Associatie van genetische variatie in CYP1A2 en UGT1A4 met metabole stoornissen bij gebruikers van clozapine en olanzapine. PW Wetenschappelijk Platform 2013; 7a1310.

Date 13-09-2021

CYP1A2*1C/heterozygoot: olanzapine

This is NOT a gene-drug interaction.

Literature:

2. 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.

Date 13-09-2021

CYP1A2*1C/*1C: olanzapine

This is NOT a gene-drug interaction.

Literature:


Date 13-09-2021

CYP1A2*1C/*1C: olanzapine

This is NOT a gene-drug interaction.

Literature:


Date 13-09-2021

CYP2D6 IM: olanzapine

This is NOT a gene-drug interaction.

Literature:


Date 13-09-2021

CYP2D6 PM: olanzapine

This is NOT a gene-drug interaction.

Literature:


Date 13-09-2021

CYP2D6 UM: olanzapine
Literature:


Date 13-09-2021

CYP2C19 IM: omeprazol

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:

29. SmPC Prilosec (VS).

Date 05-03-2018

CYP2C19 PM: omeprazol

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:

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


HLA-B*1502: oxcarbazepine

Steven's-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 weight 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:

CYP2D6 IM: oxycodon

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:

CYP2D6 PM: oxycodon

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

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

**CYP2C19 PM: 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:**

**CYP2C19 UM: pantoprazol**

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

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

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

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

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.

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.

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.

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

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.

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 (80% 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

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 (50% of the standard maximum dose):
  - 12 years and older: 10 mg/day
  - younger than 12 years: 0.08 mg/kg per day to a maximum of 3 mg/day

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.

Date 13-09-2021

CYP2C19 IM: prasugrel

This is NOT a gene-drug interaction.

Date 13-09-2021

CYP2C19 IM: prasugrel

This is NOT a gene-drug interaction.
Recommendation:
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.

Literature:
8. SPC Efient (NL en VS).

Date 19-11-2018

CYP2C19 UM: prasugrel

This is NOT a gene-drug interaction.

Literature:
2. SPC Efient (NL en VS).

Date 19-11-2018

CYP2C19 PM: prasugrel

This is NOT a gene-drug interaction.

Literature:
7. Spiekermann ES et al. Antiarrhythmic drugs that are hardly if at all metabolised by CYP2D6 include, for example, sotalol, disopyramide, quinidine and amiodarone.

Literature:
CYP2D6 UM: propafenone

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:

1. Either monitor plasma concentrations, perform an ECG and be alert to reduced efficacy of the therapy.
2. Or choose an alternative
   - Antiarrhythmic 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. Khashal 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:


Date 13-09-2021

CYP3A4: quetiapine

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

• indication DEPRESSION
  * choose an alternative
  Aripiprazole appears to be less dependent on CYP3A4 for metabolism. Olanzapine is not metabolised by CYP3A4.

• OTHER INDICATIONS
  * use 30% of the standard dose

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. Aritzume 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:


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:


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:


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:


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:


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.
CYP2C19 UM: rabeprazole

NO action is required for this gene-drug interaction.

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 and EM patients also makes differences in effectiveness between UM and EM patients less likely.

### Literature

10. 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.
29. 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 2004;19:113-22.
30. Shimazaki T et al. Rabeprazole 10 mg twice daily is superior to 20 mg once daily for night-time gastric acid suppression. Aliment Pharmacol Ther 2004;19:113-22.
36. SPC’s Paries et Aciphex (VS).

Date 05-03-2018
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.

However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.

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.

NO action is needed for this gene-drug interaction.

CYP2D6 IM: risperidone

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.

CYP2D6 PM: risperidone

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. Ganci L et al. ABCB1, ABCG2 and CYP2D6 polymorphism effects on disposition and response to long-acting risperidone. Prog Neuropsychopharmacol Biol Psychiatry 2021;104:110042.
1. Gaozi L et al. ABCB1, ABCG2 and CYP2D6 polymorphism effects on disposition and response to long-acting risperidone. Prog Neuropsychopharmacol Biol Psychiatry 2021;104:110042.
19. de Leon J et al. A study of genetic (CYP2D6 and ABCB1) and environmental (drug inhibitors and inducers) variables that may influence plasma risperidone levels. Pharmacopocyharmacology 2007;40:93-102.
26. SmPC’s Risperdal (NL en VS) en Risperdal Consta (NL).

Date 13-09-2021

CYP2D6 UM: risperidone

The percentage of patients with therapy failure increases from 16% to 37%. The gene variation leads to a high ratio of the active metabolite (9-hydroxyrisperidone (paliperidone)) compared to risperidone, which crosses the blood-brain barrier more effectively.

- choose an alternative or titrate the dose according to the maximum dose for the active metabolite (paliperidone) (oral 12 mg/day for adults and children from 15 years of age weighing at least 51 kg and 6 mg/day for children from 15 years of age weighing less than 51 kg, intramuscular 75 mg per 2 weeks)

Literature:

Date 13-09-2021

CYP2C19 IM: sertraline

NO action is needed for this gene-drug interaction.

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.

Literature:
7. SPC Zoloft.

Date 14-05-2018

This is NOT a gene-drug interaction.

Literature:

Date 14-05-2018

This is NOT a gene-drug interaction.

Literature:

Date 14-05-2018

This is NOT a gene-drug interaction.

Literature:
SLCO1B1 521CC: simvastatin

When using simvastatin 80 mg/day, the risk of myopathy is increased 30-fold to 1% 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
   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 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 CYP34A inhibitors.

Literature:

2. Wu X et al. Associations of the SLCO1B1 polymorphisms with hepatic function, baseline lipid levels, and lipid-lowering response to simvastatin in patients with hyperlipidemia. Clin Appl Thromb Hemost 2018;24:2405S-247S.
20. SmPC Zocor.

Date 18-05-2020

SLCO1B1 521CT: 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 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 CYP34A 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:

2. Wu X et al. Associations of the SLCO1B1 polymorphisms with hepatic function, baseline lipid levels, and lipid-lowering response to simvastatin in patients with hyperlipidemia. Clin Appl Thromb Hemost 2018;24:2405S-247S.
8. de Keyser 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.
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).

Date 12-03-2020

**CYP2C9*2/*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).

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 12-09-2022

**CYP2D6 IM: sotalol**

This is NOT a gene-drug interaction.

**Literature:**

- 

Date 12-09-2022

**CYP2D6 PM: sotalol**

This is NOT a gene-drug interaction.

**Literature:**

- 

Date 12-09-2022

**CYP2D6 UM: sotalol**

This is NOT a gene-drug interaction.

**Literature:**

- 

Date 12-09-2022

**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.
**CYP3A5 homozygote 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 outcomes. The genetic variation increases in an improved conversion of tacrolimus to inactive metabolites and therefore a higher required dose.

- **Indicators OTHER than liver transplantation:** 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 5 homozygous kidney transplant patients. Their target value was 10 - 15 ng/mL.

- **LIVER transplantation:**

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

**Literature:**

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

Date 03-02-2020

1602

CYP2D6 IM: 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 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 result can be reduced in 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:

1. Welzen ME et al. The effect of tamoxifen dose increment in patients with impaired CYP2D6 activity, Ther Drug Monit 2015;37:501-7
5. Lam DW et al. CYP2D6 genotype and tamoxifen response for breast cancer: a systematic review and meta-analysis, PLoS One 2013;8:e79648
31. SPC Tamoxifen PCH.
A patient with undetectable DPD activity tolerated 0.43% of the standard capecitabine dose (150 mg every 5 days with every third dose skipped).

**DPD AS 1.5: tegafur**

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.

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.

**DPD FENO: tegafur**

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.

Fluorouracil and capecitabine, starting with 50% of the standard dose is recommended and the dose should then be adjusted based on toxicity and effectiveness.

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

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.

**CYP2C19 IM: ticagrelor**

This is NOT a gene-drug interaction.
CYP2C9 PM: ticagrelor

This is NOT a gene-drug interaction.

Literature:


CYP2C9 UM: ticagrelor

This is NOT a gene-drug interaction.

Literature:


NUDT15 DM: tioguanine

Grade ≥ 2 leukopenia 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.

Note: The percentage of 75% is based on the analogy with TPMT, for which the gene variants have a comparable effect on toxicity to those of NUDT15.

• 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.

Note: The percentage of 75% is based on the analogy with TPMT, for which the gene variants have a comparable effect on toxicity to those of NUDT15.

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

Literature:


11. LEUKAEMIA:
  - start with 75% of the standard dose

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

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11. LEUKAEMIA:
  - start with 75% of the standard dose

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

Grade ≥ 2 leukoapenia occurs in an estimated 95% of these patients with standard therapy. The genetic variation increases the concentration of the fully activated metabolite of tioguanine.

- avoid tioguanine
- if it is not possible to avoid tioguanine: 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.

**TPMT IM: tioguanine**

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
- LEUKÆMIA:
  - 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

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

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

**Literature:**


**TPMT PM: tioguanine**

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:**

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

NO action is required for this gene-drug interaction.

Literature:

NO action is required for this gene-drug interaction.

There are no clinical consequences of the increased tolbutamide plasma concentration.

Literature:

NO action is required for this gene-drug interaction.

There are no clinical consequences of the increased tolbutamide plasma concentration.

Literature:
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.

Recommendation:

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.

Oxycodone 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
**Date 20-11-2017**

### 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. **1. be alert to a reduced effectiveness**
2. **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.**

Oxycodone 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

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**Literature:**


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**Date 20-11-2017**

### 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.
  - Oxycodone 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:
  - use 40% of the standard dose
  - advise the patient to report side effects (such as drowsiness, confusion, constipation, nausea and vomiting, respiratory depression or urine retention).

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**Literature:**

9. 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.

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.

**Literature:**


Date 14-11-2022

**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.

Furthermore, a reduced effectiveness of venlafaxine has been observed in depression patients with this gene variation.

**Literature:**

CYP2D6 UM: voriconazole

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

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

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

CYP2C19 IM: voriconazol

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

- monitor the plasma concentration

Literature:

25. Kim SH et al. Clinical impact of cytochrome P450 2C19 genotype on the treatment of invasive aspergillosis under routine therapeutic drug monitoring in a
CYP2C19 UM: voriconazol

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

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

**Literature:**

9. SPC Coumadin (VS).

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-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.

**Literature:**

9. SPC Coumadin (VS).

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-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.

**Literature:**

9. SPC Coumadin (VS).

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 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.

**Literature:**

9. SPC Coumadin (VS).
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.

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/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.

Literature:
9. SPC Coumadin (VS).

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.

Literature:
9. SPC Coumadin (VS).

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. SPC 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. SPC 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:

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:
5. SmPC’s Cisordinol en Cisordinol Depot.

Date 13-09-2021

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.