HLA-B*5701: abacavir 2356

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:

1. Sousa-Pinto B et al. Pharmacogenetics of abacavir hypersensitivity: a systematic review and meta-analysis of the association with HLA-B*57:01. J Allergy Clin Immunol 2015;136:1092-4.e3.
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17. SmPC Ziagen (NL en VS).

Date 13-05-2019

CYP2C9 IM: acenocoumarol 1868

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:

1. Varnai R et al. CYP2C9 and VKORC1 in therapeutic dosing and safety of acenocoumarol treatment: implication for clinical practice in Hungary. Environ Toxicol Pharmacol 2017;56:282-289.
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Date 14-05-2018

CYP2C9 PM: acenocoumarol 1869

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).

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Date 14-05-2018

CYP2C9*1/*2: acenocoumarol **1863**

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).

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Date 14-05-2018

CYP2C9*1/*3: acenocoumarol **1864**

NO action is needed for this gene-drug interaction.

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

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Date 14-05-2018

CYP2C9*2/*2: acenocoumarol **1865**

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Date 14-05-2018

CYP2C9*2/*3: acenocoumarol **1866**

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:

1. Varnai R et al. CYP2C9 and VKORC1 in therapeutic dosing and safety of acenocoumarol treatment: implication for clinical practice in Hungary. Environ Toxicol Pharmacol 2017;56:282-289.
2. Kalpana SR et al. Influence of VKORC1 and CYP2C9 polymorphisms on daily acenocoumarol dose requirement in South Indian patients with mechanical heart valves. Clin Appl Thromb Hemost 2017;23: 876-882.
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6. Jiménez-Varo E et al. Pharmacogenetics role in the safety of acenocoumarol therapy. Thromb Haemost 2014;112:522-36.
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8. Verhoef TI et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med 2013;369:2304-12.
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10. Gschwind L et al. Impact of CYP2C9 polymorphisms on the vulnerability to pharmacokinetic drug-drug interactions during acenocoumarol treatment. Pharmacogenomics 2013:14;745-53.
11. Verhoef TI et al. Long-term anticoagulant effects of the CYP2C9 and VKORC1 genotypes in acenocoumarol users. J Thromb Haemost 2012;10:606-14.
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13. Cadamuro J et al. Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. Eur J Clin Pharmacol 2010;66:253-60.
14. Wijnen PA et al. Variant VKORC1 and CYP2C9 alleles in patients with diffuse alveolar hemorrhage caused by oral anticoagulants. Mol Diagn Ther 2010;14:23-30.
15. Teichert M et al. Genotypes associated with reduced activity of VKORC1 and CYP2C9 and their modification of acenocoumarol anticoagulation during the initial treatment period. Clin Pharmacol Ther 2009;85:379-86.
16. Montes R et al. The influence of polymorphisms of VKORC1 and CYP2C9 on major gastrointestinal bleeding risk in anticoagulated patients. Br J Haematol 2008;143:727-33.
17. Markatos CN et al. VKORC1 and CYP2C9 allelic variants influence acenocoumarol dose requirements in Greek patients. Pharmacogenomics 2008;9:1631-8.
18. Spreafico M et al. Effects of CYP2C9 and VKORC1 on INR variations and dose requirements during initial phase of anticoagulant therapy. Pharmacogenomics 2008;9:1237-50.
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25. Morin S et al. Pharmacogenetics of acenocoumarol pharmacodynamics. Clin Pharmacol Ther 2004;75:403-14.
26. Schalekamp T et al. Acenocoumarol stabilization is delayed in CYP2C9*3 carriers. Clin Pharmacol Ther 2004;75:394-402.
27. Visser LE et al. The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics 2004;1427-33.
28. Thijssen HH et al. Acenocoumarol pharmacokinetics in relation to cytochrome P450 2C9 genotype. Clin Pharmacol Ther 2003;7461-8.

29. Verstuyft C et al. Genetic and environmental risk factors for oral anticoagulant overdose. Eur J Clin Pharmacol 2003;58:739-45.
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31. Thijssen HH et al. The possession of the CYP2C9*3 allele is associated with low dose requirement of acenocoumarol. Pharmacogenetics 2000;10:757-60.

Date 14-05-2018

CYP2C9*3/*3: acenocoumarol **1867**

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:

1. Varnai R et al. CYP2C9 and VKORC1 in therapeutic dosing and safety of acenocoumarol treatment: implication for clinical practice in Hungary. Environ Toxicol Pharmacol 2017;56:282-289.
2. Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464.
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5. Verhoef TI et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med 2013;369:2304-12.
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13. Montes R et al. The influence of polymorphisms of VKORC1 and CYP2C9 on major gastrointestinal bleeding risk in anticoagulated patients. Br J Haematol 2008;143:727-33.
14. Spreafico M et al. Effects of CYP2C9 and VKORC1 on INR variations and dose requirements during initial phase of anticoagulant therapy. Pharmacogenomics 2008;9:1237-50.
15. González-Conejero R et al. The genetic interaction between VKORC1 c1173t and calumenin a29809g modulates the anticoagulant response of acenocoumarol. J Thromb Haemost 2007;5:1701-6.
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Date 14-05-2018

VKORC1 -1639 AA: acenocoumarol **1910**

An INR $\geq$ 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.
A (non-validated) algorithm has been prescribed for children that should result in a better prediction of the maintenance dose for AA than the current guideline used by the Anticoagulation Clinic (Maagdenberg H et al. The pediatric acenocoumarol dosing algorithm: The Children Anticoagulation and Pharmacogenetics Study. J Thromb Haemost 2018 Jun 23 [Epub ahead of print]. PubMed PMID: 29935043).

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Date 10-09-2018

VKORC1 -1639 GA: acenocoumarol **1909**

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:

1. Cerezo-Manchado JJ et al. Effect of VKORC1, CYP2C9 and CYP4F2 genetic variants in early outcomes during acenocoumarol treatment. Pharmacogenomics 2014; 15: 987-96.
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Date 10-09-2018

CYP2D6 IM: amiodaron **2543**

This is NOT a gene-drug interaction.

Literature:
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Date 24-08-2016

CYP2D6 PM: amiodaron **2542**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2D6 UM: amiodaron **2544**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2C19 IM: amitriptyline **7024**

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:

1. Ryu S et al. A study on CYP2C19 and CYP2D6 polymorphic effects on pharmacokinetics and pharmacodynamics of amitriptyline in healthy Koreans. Clin Transl Sci 2017;10:93-101.
2. Atasayar G et al. Association of MDR1, CYP2D6, and CYP2C19 gene polymorphisms with prophylactic migraine treatment response. J Neurol Sci 2016;366:149-154.
3. De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
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7. Shimoda K et al. The impact of CYP2C19 and CYP2D6 genotypes on metabolism of amitriptyline in Japanese psychiatric patients. J Clin Psychopharmacol 2002;22:371-8.
8. Jiang ZP et al. The role of CYP2C19 in amitriptyline N-demethylation in Chinese subjects. Eur J Clin Pharmacol 2002;58:109-13.

Date 04-03-2019

CYP2C19 PM: amitriptyline **7025**

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:

1. Ryu S et al. A study on CYP2C19 and CYP2D6 polymorphic effects on pharmacokinetics and pharmacodynamics of amitriptyline in healthy Koreans. Clin Transl Sci 2017;10:93-101.
2. De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
3. van der Weide J et al. Metabolic ratios of psychotropics as indication of cytochrome P450 2D6/2C19 genotype. Ther Drug Monit 2005;27:478-83.
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6. Shimoda K et al. The impact of CYP2C19 and CYP2D6 genotypes on metabolism of amitriptyline in Japanese psychiatric patients. J Clin Psychopharmacol 2002;22:371-8.
7. Jiang ZP et al. The role of CYP2C19 in amitriptyline N-demethylation in Chinese subjects. Eur J Clin Pharmacol 2002;58:109-13.
8. SmPC Amitriptyline HCl Apotex.

Date 04-03-2019

CYP2C19 UM: amitriptyline **7026**

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:

1. De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.

Date 04-03-2019

CYP2D6 IM: amitriptyline **1920**

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:

1. Chaudhry M et al. Impact of CYP2D6 genotype on amitriptyline efficacy for the treatment of diabetic peripheral neuropathy: a pilot study. Pharmacogenomics 2017;18:433-443.
2. Ryu S et al. A study on CYP2C19 and CYP2D6 polymorphic effects on pharmacokinetics and pharmacodynamics of amitriptyline in healthy Koreans. Clin Transl Sci 2017;10:93-101.
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9. Breyer-Pfaff U et al. Enantioselective amitriptyline metabolism in patients phenotyped for two cytochrome P450 isozymes. Clin Pharmacol Ther 1992;52:350-8.
10. Mellstrom B et al. Amitriptyline metabolism: association with debrisoquin hydroxylation in nonsmokers. Clin Pharmacol Ther 1986;39:369-71.
11. Baumann P et al. Amitriptyline pharmacokinetics and clinical response: II. Metabolic polymorphism assessed by hydroxylation of debrisoquine and mephenytoin. Int Clin Psychopharmacol 1986;1:102-12.

Date 10-09-2018

CYP2D6 PM: amitriptyline **1921**

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

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

Literature:

1. Atasayar G et al. Association of MDR1, CYP2D6, and CYP2C19 gene polymorphisms with prophylactic migraine treatment response. J Neurol Sci 2016;366:149-154.
2. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
3. Halling J et al. The CYP2D6 polymorphism in relation to the metabolism of amitriptyline and nortriptyline in the Faroese population. Br J Clin Pharmacol 2008;65:134-8.
4. Koski A et al. CYP2D6 and CYP2C19 genotypes and amitriptyline metabolite ratios in a series of medicolegal autopsies. Forensic Sci Int 2006;158:177-83.
5. Steimer W et al. Amitriptyline or not, that is the question: pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy. Clin Chem 2005;51:376-85.
6. Breyer-Pfaff U et al. Enantioselective amitriptyline metabolism in patients phenotyped for two cytochrome P450 isozymes. Clin Pharmacol Ther 1992;52:350-8.
7. Mellstrom B et al. Amitriptyline metabolism: association with debrisoquin hydroxylation in nonsmokers. Clin Pharmacol Ther 1986;39:369-71.
8. Baumann P et al. Amitriptyline pharmacokinetics and clinical response: II. Metabolic polymorphism assessed by hydroxylation of debrisoquine and mephenytoin. Int Clin Psychopharmacol 1986;1:102-12.
9. SmPC's Amitriptyline HCl Apotex (NL) en Amitriptyline Hydrochloride Sandoz (VS).

Date 10-09-2018

CYP2D6 UM: amitriptyline **1922**

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

- increase the dose to 1.4 times the standard dose, monitor the effect and side effects or the plasma concentrations and be alert to increased plasma concentrations of the cardiotoxic Z-10-hydroxy metabolites. Plasma concentrations of Z-hydroxy nortriptyline or Z-hydroxy amitriptyline higher than 40 ng/mL are considered toxic.
- if a dose increase is not desirable due to the cardiotoxic hydroxy metabolite: avoid amitriptyline Anti-depressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Literature:

1. Chaudhry M et al. Impact of CYP2D6 genotype on amitriptyline efficacy for the treatment of diabetic peripheral neuropathy: a pilot study. Pharmacogenomics 2017;18:433-443.
2. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
3. Steimer W et al. Allele-specific change of concentration and functional gene dose for the prediction of steady-state serum concentrations of amitriptyline and nortriptyline in CYP2C19 and CYP2D6 extensive and intermediate metabolizers. Clin Chem 2004;50:1623-33.
4. Grasmader K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.
5. Bertilsson L et al. Extremely rapid hydroxylation of debrisoquine: a case report with implication for treatment with nortriptyline and other tricyclic antidepressants. Ther Drug Monit 1985;7:478-80.
6. Baumann P et al. Amitriptyline pharmacokinetics and clinical response: II. Metabolic polymorphism assessed by hydroxylation of debrisoquine and mephenytoin. Int Clin Psychopharmacol 1986;1:102-12.

Date 10-09-2018

Fact. V Leiden heterozyg: anticoncept. met oestr. **1567**

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

Recommendation:

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

Literature:

1. Dulicek P et al. Venous thromboembolism in young female while on oral contraceptives: frequency of inherited thrombophilia and analysis of thrombosis in 400 Czech women. Clin Appl Thromb Hemost 2008 Dec 30 (Epub ahead of print).
2. Celikel S et al. Hereditary angioedema associated with heterozygous factor V Leiden mutation in a patient with Purpura fulminans. Int Arch Allergy Immunol 2007;142:175-8.
3. Couturaud F et al. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. Thromb Haemost 2006;96:744-9.
4. Martinelli I et al. Oral contraceptive use, thrombophilia and their interaction in young women with ischemic stroke. Haematologica 2006;91:844-7.
5. Wu O et al. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess 2006;10:1-110.
6. Schreijer AJ et al. Activation of coagulation system during air travel: a crossover study. Lancet 2006;367:832-8.
7. Osmanağaoğlu MA et al. Skin venous thromboembolism by combined oral contraceptive in a woman with acquired angioedema and Factor V Leiden mutation. Contraception 2006;73:311-4.
8. Slooter AJ et al. Prothrombotic conditions, oral contraceptives, and the risk of ischemic stroke. J Thromb Haemost 2005;3:1213-7.
9. Girolami A et al. Long term use of oral contraceptives without thrombosis in patients with FV Leiden polymorphism: a study of 37 patients (2 homozygous and 35 heterozygous). J Thromb Thrombolysis 2004;17:145-9.
10. Martinelli I et al. Risk factors and recurrence rate of primary deep vein thrombosis of the upper extremities. Circulation 2004;110:566-70.
11. Sidney S et al. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. Contraception 2004;70:3-10.
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13. Kemmeren JM et al. Effect of second- and third-generation oral contraceptives on the protein C system in the absence or presence of the factor V Leiden mutation: a randomized trial. Blood 2004;103:927-33.
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15. Kemmeren JM et al. Effects of second and third generation oral contraceptives and their respective progestagens on the coagulation system in the absence or presence of the factor V Leiden mutation. Thromb Haemost 2002;87:199-205.
16. Legnani C et al. Venous thromboembolism in young women: role of thrombophilic mutations and oral contraceptive use. Eur Heart J 2002;23:984-90.
17. Emmerich J et al. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism - pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Thromb Haemost 2001;86:809-16.
18. Bloemenkamp KW et al. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet 1995;346:1593-6.
19. Vandenbroucke JP et al. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 1994;344:1453-7.
20. CBO Richtlijn Diagnostiek, Preventie en Behandeling van Veneuze Trombo-embolie en Secundaire Preventie Arteriële Trombose 2009. www.cbo.nl.

Date 08-06-2005

Fact. V Leiden homozyg: anticoncept. met oestr. **1566**

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

Recommendation:

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

Literature:

1. Dulicek P et al. Venous thromboembolism in young female while on oral contraceptives: frequency of inherited thrombophilia and analysis of thrombosis in 400 Czech women. Clin Appl Thromb Hemost 2008 Dec 30 (Epub ahead of print).
2. Couturaud F et al. Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. Thromb Haemost 2006;96:744-9.
3. Wu O et al. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess 2006;10:1-110.
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7. Ehrenforth et al. Impact of environmental and hereditary risk factors on the clinical manifestation of thrombophilia in homozygous carriers of factor V:G1691A. J Thromb Haemost 2004;2:430-6.
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10. Bloemenkamp KW et al. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet 1995;346:1593-6.
11. CBO Richtlijn Diagnostiek, Preventie en Behandeling van Veneuze Trombo-embolie en Secundaire Preventie Arteriële Trombose 2009. www.cbo.nl.

Date 08-06-2005

CYP2D6 IM: aripiprazol **1541**

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.

Literature:

1. Belmonte C et al. Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 polymorphisms on pharmacokinetics and safety of aripiprazole in healthy volunteers. Basic Clin Pharmacol Toxicol 2018 Jan 11 [Epub ahead of print].
2. Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84.
3. 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.
4. Suzuki T et al. Effects of genetic polymorphisms of CYP2D6, CYP3A5, and ABCB1 on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. Ther Drug Monit 2014;36:651-5.
5. Suzuki T et al. Effects of the CYP-2D6*10 allele on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. Ther Drug Monit 2011;33:21-4.
6. Hendset M et al. Impact of the CYP2D6 genotype on steady-state serum concentrations of aripiprazole and dehydroaripiprazole. Eur J Clin Pharmacol 2007;63:1147-51.
7. Kubo M et al. Pharmacokinetics of aripiprazole, a new antipsychotic, following oral dosing in healthy adult Japanese volunteers: influence of CYP2D6 polymorphism. Drug Metab Pharmacokinet 2007;22:358-66.
8. Kim E et al. Effects of DRD2 and CYP2D6 genotypes on delta EEG power response to aripiprazole in healthy male volunteers: a preliminary study. Hum Psychopharmacol 2006;21:519-28.
9. Kubo M et al. Influence of itraconazole co-administration and CYP2D6 genotype on the pharmacokinetics of the new antipsychotic aripiprazole. Drug Metab Pharmacokinet 2005;20:55-64.

Date 14-05-2018

CYP2D6 PM: aripiprazol **1542**

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 (67-75% of the standard maximum dose of aripiprazole).

Literature:

1. Belmonte C et al. Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 polymorphisms on pharmacokinetics and safety of aripiprazole in healthy volunteers. Basic Clin Pharmacol Toxicol 2018 Jan 11 [Epub ahead of print].
2. Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84.
3. 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.
4. Hendset M et al. Impact of the CYP2D6 genotype on steady-state serum concentrations of aripiprazole and dehydroaripiprazole. Eur J Clin Pharmacol 2007;63:1147-51.
5. Oosterhuis M et al. Safety of aripiprazole: high serum levels in a CYP2D6 mutated patient. Am J Psychiatry 2007;164:175.
6. SPC's Abilify, Abilify Maintena, Abilify (USA), Aristad (USA).

Date 14-05-2018

CYP2D6 UM: aripiprazol **1543**

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:

1. Belmonte C et al. Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 polymorphisms on pharmacokinetics and safety of aripiprazole in healthy volunteers. Basic Clin Pharmacol Toxicol 2018 Jan 11 [Epub ahead of print].
2. Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84.
3. 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.

Date 14-05-2018

CYP2D6 IM: atenolol **2454**

This is NOT a gene-drug interaction.

Literature:

1. Bijl MJ et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. Clin Pharmacol Ther 2009;85:45-50.

Date 26-05-2009

CYP2D6 PM: atenolol **2453**

This is NOT a gene-drug interaction.

Literature:

1. Bijl MJ et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. Clin Pharmacol Ther 2009;85:45-50.
2. Lewis RV et al. Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics. Br J Clin Pharmacol 1985;19:329-33.
3. Dayer P et al. Interindividual variation of beta-adrenoceptor blocking drugs, plasma concentration and effect: influence of genetic status on behaviour of atenolol, bopindolol and metoprolol. Eur J Clin Pharmacol 1985;28:149-53.
4. Freestone S et al. Comparison of two long-acting preparations of metoprolol with conventional metoprolol and atenolol in healthy men during chronic dosing. Br J Clin Pharmacol 1982;14:713-8.

Date 26-05-2009

CYP2D6 UM: atenolol **2455**

This is NOT a gene-drug interaction.

Literature:
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Date 26-05-2009

CYP2D6 IM: atomoxetine **1599**

The genetic variation increases the plasma concentration of atomoxetine and can thereby reduce the dose requirement.

Recommendation:

1. 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 2-3 times higher for IM than for EM at the same dose.

Literature:

1. Brown JT et al. Single dose, CYP2D6 genotype-stratified pharmacokinetic study of atomoxetine in children with ADHD. Clin Pharmacol Ther 2016;99:642-50.
2. Byeon JY et al. Effects of the CYP2D6*10 allele on the pharmacokinetics of atomoxetine and its metabolites. Arch Pharm Res 2015;38:2083-91.
3. Fijal BA et al. CYP2D6 predicted metabolizer status and safety in adult patients with attention-deficit hyperactivity disorder participating in a large placebo-controlled atomoxetine maintenance of response clinical trial. J Clin Pharmacol 2015;55:1167-74.
4. Matsui A et al. Pharmacokinetics, safety, and tolerability of atomoxetine and effect of CYP2D6*10*/10 genotype in healthy Japanese men. J Clin Pharmacol 2012;52:388-403.
5. ter Laak MA et al. Recognition of impaired atomoxetine metabolism because of low CYP2D6 activity. Pediatr Neurol 2010;43:159-62.
6. Cui YM et al. Atomoxetine pharmacokinetics in healthy Chinese subjects and effect of the CYP2D6*10 allele. Br J Clin Pharmacol 2007;64:445-9.

Date 31-10-2016

CYP2D6 PM: atomoxetine **1598**

The genetic variation increases the plasma concentration of atomoxetine and thereby the risk of side effects.

Recommendation:

1. start with the normal initial dose, bearing in mind that an increase in this dose probably will not be required
2. advise the patient to seek contact if side effects occur (such as decreased appetite, vomiting, abdominal pain, constipation, insomnia, early waking, drowsiness, irritability, pupil dilation and itching)
3. 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 8-11 times higher for PM than for EM at the same dose.

Literature:

1. Brown JT et al. Single dose, CYP2D6 genotype-stratified pharmacokinetic study of atomoxetine in children with ADHD. Clin Pharmacol Ther 2016;99:642-50.
2. Fijal BA et al. CYP2D6 predicted metabolizer status and safety in adult patients with attention-deficit hyperactivity disorder participating in a large placebo-controlled atomoxetine maintenance of response clinical trial. J Clin Pharmacol 2015;55:1167-74.
3. Loghin C et al. Effects of atomoxetine on the QT interval in healthy CYP2D6 poor metabolizers. Br J Clin Pharmacol 2013;75:538-49.
4. Matsui A et al. Pharmacokinetics, safety, and tolerability of atomoxetine and effect of CYP2D6*10*/10 genotype in healthy Japanese men. J Clin Pharmacol 2012;52:388-403.
5. Ramoz N et al. A Haplotype of the Norepinephrine Transporter (Net) Gene Slc6a2 is Associated with Clinical Response to Atomoxetine in Attention-Deficit Hyperactivity Disorder (ADHD). Neuropsychopharmacology 2009;34:2135-42.
6. Trzepacz PT et al. CYP2D6 metabolizer status and atomoxetine dosing in children and adolescents with ADHD. Eur Neuropsychopharmacol 2008;18:79-86.
7. Cui YM et al. Atomoxetine pharmacokinetics in healthy Chinese subjects and effect of the CYP2D6*10 Michelson D et al. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry 2007;46:242-51.
8. Sauer JM et al. Disposition and metabolic fate of atomoxetine hydrochloride: the role of CYP2D6 in human disposition and metabolism. Drug Metab Dispos 2003;31:98-107.
9. SPC's Strattera (NL en VS).
10. Data on file, Lilly Research Laboratories, 2006. Atomoxetine - comparison of data of extensive metaboliser and poor metaboliser patients.

Date 31-10-2016

CYP2D6 UM: atomoxetine **1600**

The genetic variation results in an increased conversion of atomoxetine to the active metabolite 4-hydroxyatomoxetine, which has a much lower plasma concentration. As the plasma concentration of the active ingredients decreases as a result, this gene variation can result in reduced efficacy.

Recommendation:

1. be extra alert to reduced efficacy of the treatment
2. advise the patient to contact their doctor in the event of inadequate effect
3. an alternative can be selected as a precaution
   Clonidine is not metabolised by CYP2D6.

Literature:

1. Brown JT et al. Single dose, CYP2D6 genotype-stratified pharmacokinetic study of atomoxetine in children with ADHD. Clin Pharmacol Ther 2016;99:642-50.

Date 31-10-2016

SLCO1B1 521CC: atorvastatine **4058**

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.

- Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy:
  1. Choose an alternative
     Do not select simvastatin, as this is also affected by the SLCO1B1 gene variation. Rosuvastatin and pravastatin are influenced to a similar extent by SLCO1B1 polymorphisms, but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not influenced significantly by SLCO1B1 gene variation or CYP3A4 inhibitors.
  2. If an alternative is not an option: advise the patient to contact their doctor in the event of muscle symptoms.
- Patient has NO additional significant risk factors for statin-induced myopathy:
  1. Advise the patient to contact their doctor in the event of muscle symptoms.

Literature:

1. Turner RM et al. A genome-wide association study of circulating levels of atorvastatin and its major metabolites. Clin Pharmacol Ther 2020 Mar 3 [Epub ahead of print].
2. Liu JE et al. SLCO1B1 521T > C polymorphism associated with rosuvastatin-induced myotoxicity in Chinese coronary artery disease patients: a nested case-control study. Eur J Clin Pharmacol 2017;73:1409-16.
3. Jiang J et al. Association between SLCO1B1 -521T>C and -388A>G polymorphisms and risk of statin-induced adverse drug reactions: a meta-analysis. Springerplus 2016;5:1368.
4. Fukunaga K et al. ABCB1 polymorphism is associated with atorvastatin-induced liver injury in Japanese population. BMC Genet 2016;17:79.
5. Hou Q et al. Association between SLCO1B1 gene T521C polymorphism and statin-related myopathy risk: a meta-analysis of case-control studies. Medicine (Baltimore) 2015;94:e1268.
6. Giannakopoulou E et al. No impact of SLCO1B1 521 T>C, 388A>G and 411G>A polymorphisms on response to statin therapy in the Greek population. Mol Biol Rep 2014;41:4631-8.
7. de Keyser CE et al. The SLCO1B1 c.521T>C polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. Pharmacogenet Genomics 2014;24:43-51.
8. Fu Q et al. Lack of association between SLCO1B1 polymorphism and the lipid-lowering effects of atorvastatin and simvastatin in Chinese individuals. Eur J Clin Pharmacol 2013;69:1269-74.
9. Carr DF et al. SLCO1B1 genetic variant associated with statin-induced myopathy: a proof-of-concept study using the Clinical Practice Research Datalink. Clin Pharmacol Ther 2013;94:695-701.
10. Francesca Notarangelo M et al. Genetic predisposition to atorvastatin-induced myopathy: a case report. J Clin Pharm Ther 2012;37:604-6.
11. Brunham LR et al. Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. Pharmacogenomics J 2012;12:233-7.
12. Santos PC et al. SLCO1B1 haplotypes are not associated with atorvastatin-induced myalgia in Brazilian patients with familial hypercholesterolemia. Eur J Clin Pharmacol 2012;68:273-9.
13. Rodrigues AC et al. Pharmacogenetics of OATP transporters reveals that SLCO1B1 c.388A>G variant is determinant of increased atorvastatin response. Int J Mol Sci 2011;12:5815-27.
14. Puccetti L et al. Genetic involvement in statins induced myopathy. Preliminary data from an observational case-control study. Atherosclerosis 2010;211:28-9.
15. Lee YJ et al. Effects of SLCO1B1 and ABCB1 genotypes on the pharmacokinetics of atorvastatin and 2-hydroxyatorvastatin in healthy Korean subjects. Int J Clin Pharmacol Ther 2010;48:36-45.
16. Voora D et al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol 2009;54:1609-16.
17. Mega JL et al. Identification of genetic variants associated with response to statin therapy. Arterioscler Thromb Vasc Biol 2009;29:1310-5.
18. He YJ et al. Rifampicin alters atorvastatin plasma concentration on the basis of SLCO1B1 521T>C polymorphism. Clin Chim Acta 2009;405:49-52.
19. Pasanen MK et al. Polymorphism of the hepatic influx transporter organic anion transporting polypeptide 1B1 is associated with increased cholesterol synthesis rate. Pharmacogenet Genomics 2008;18:921-6.
20. Pasanen MK et al. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2007;82:726-3
21. Hermann M et al. Exposure of atorvastatin is unchanged but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy. Clin Pharmacol Ther 2006;79:532-9.
22. Thompson JF et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharmacogenomics J 2005;5:352-8.
23. SmPC Lipitor.

Date 18-05-2020

SLCO1B1 521TC: atorvastatine **4057**

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.

- Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy:
  1. Choose an alternative
     Rosuvastatin and pravastatin are influenced to a similar extent by the SLCO1B1 gene variation, but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.
     Fluvastatin is not influenced significantly by the SLCO1B1 gene variation or CYP3A4 inhibitors.
  2. If an alternative is not an option: advise the patient to contact their doctor in the event of muscle symptoms.
- Patient has NO additional significant risk factors for statin-induced myopathy:
  1. Advise the patient to contact their doctor in the event of muscle symptoms.

Literature:

1. Turner RM et al. A genome-wide association study of circulating levels of atorvastatin and its major metabolites. Clin Pharmacol Ther 2020 Mar 3 [Epub ahead of print].
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Date 18-05-2020

NUDT15 IM: azathioprine/mercaptopurine **7035**

Grade ≥ 2 leukopaenia 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:

1. Zhu Y et al. Combination of common and novel rare NUDT15 variants improves predictive sensitivity of thiopurine-induced leukopenia in children with acute lymphoblastic leukemia. Haematologica 2018 Mar 8 [Epub ahead of print].
2. Zhang AL et al. Association of NUDT15 c.415C>T allele and thiopurine-induced leukocytopenia in Asians: a systematic review and meta-analysis. Ir J Med Sci 2018;187:145-153.
3. Yi ES et al. NUDT15 variants cause hematopoietic toxicity with low 6-TGN levels in children with acute lymphoblastic leukemia. Cancer Res Treat 2017 Sep 13 [Epub ahead of print].
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7. Liang DC et al. NUDT15 gene polymorphism related to mercaptopurine intolerance in Taiwan Chinese children with acute lymphoblastic leukemia. Pharmacogenomics J 2016;16:536-9.
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11. Yang SK et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. Nat Genet 2014;46:1017-20.
12. SmPC's Puri-Nethol en Imuran.

Date 17-09-2019

NUDT15 PM: azathioprine/mercaptopurine **7036**

Grade ≥ 2 leukopaenia 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 adjustment 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 < 20% was calculated for NUDT15 PM, 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:

1. Zhu Y et al. Combination of common and novel rare NUDT15 variants improves predictive sensitivity of thiopurine-induced leukopenia in children with acute lymphoblastic leukemia. Haematologica 2018 Mar 8 [Epub ahead of print].
2. Zhang AL et al. Association of NUDT15 c.415C>T allele and thiopurine-induced leukocytopenia in Asians: a systematic review and meta-analysis. Ir J Med Sci 2018;187:145-153.
3. Yi ES et al. NUDT15 variants cause hematopoietic toxicity with low 6-TGN levels in children with acute lymphoblastic leukemia. Cancer Res Treat 2017 Sep 13 [Epub ahead of print].
4. Kim H et al. APEX1 polymorphism and mercaptopurine-related early onset neutropenia in pediatric acute lymphoblastic leukemia. Cancer Res Treat 2017 Sep 4 [Epub ahead of print].
5. Chao K et al. Combined detection of NUDT15 variants could highly predict thiopurine-induced leukopenia in Chinese patients with inflammatory bowel disease: a multicenter analysis. Inflamm Bowel Dis 2017;23:1592-9.
6. Yin D et al. Impact of NUDT15 polymorphisms on thiopurines-induced myelotoxicity and thiopurines tolerance dose. Oncotarget 2017;8:13575-85.
7. Liang DC et al. NUDT15 gene polymorphism related to mercaptopurine intolerance in Taiwan Chinese children with acute lymphoblastic leukemia. Pharmacogenomics J 2016;16:536-9.
8. Zhu X et al. NUDT15 polymorphisms are better than thiopurine S-methyltransferase as predictor of risk for thiopurine-induced leukopenia in Chinese patients with Crohn's disease. Aliment Pharmacol Ther 2016;44:967-75.
9. Moriyama T et al. NUDT15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity. Nat Genet 2016;48:367-73.
10. Yang JJ et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. J Clin Oncol 2015;33:1235-42.
11. Yang SK et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. Nat Genet 2014;46:1017-20.
12. SmPC's Puri-Nethol en Imuran.

Date 17-09-2019

TPMT IM: azathioprine/mercaptopurine **1905**

Grade ≥ 2 leukopaenia 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:

1. Fan X et al. NUDT15 polymorphism confer increased susceptibility to thiopurine-induced leukopenia in patients with autoimmune hepatitis and related cirrhosis. Front Pharmacol 2019;10:346.
2. Choi R et al. Pathway genes and metabolites in thiopurine therapy in Korean children with acute lymphoblastic leukaemia. Br J Clin Pharmacol 2019 Mar 30 [Epub ahead of print].
3. Eriksen PL et al. Enrichment of genetic variants in the glucocorticoid receptor signalling pathway in autoimmune hepatitis with failure of standard treatment. Basic Clin Pharmacol Toxicol 2017;121:189-94.
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12. Dong XW et al. Thiopurine S-methyltransferase polymorphisms and thiopurine toxicity in treatment of inflammatory bowel disease. World J Gastroenterol 2010;16:3187-95.
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21. Kurzawski M et al. The impact of thiopurine s-methyltransferase polymorphism on azathioprine-induced myelotoxicity in renal transplant recipients. Ther Drug Monit 2005;27:435-41.

22. Fabre MA et al. The impact of thiopurine S-methyltransferase polymorphisms on azathioprine dose 1 year after renal transplantation. Transpl Int 2004;17:531-9.
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33. Stanulla M et al. Thiopurine methyltransferase (TPMT) genotype and early treatment response to mercaptopurine in childhood acute lymphoblastic leukemia. JAMA 2005;293:1485-9.
34. Evans WE et al. Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine or azathioprine. J Clin Oncol 2001;19:2293-301.
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36. McLeod HL et al. Analysis of thiopurine methyltransferase variant alleles in childhood acute lymphoblastic leukaemia. Br J Haematol 1999;105:696-700.
37. SmPC's Imuran (VS) en Purixan (VS).

Date 17-09-2019

TPMT PM: azathioprine/mercaptopurine **1906**

Grade ≥ 2 leukopaenia and intolerance occurred in 98% of these patients with standard therapy. The gene variation increases the quantities of the active metabolites of azathioprine and mercaptopurine.

Recommendation:

- Choose an alternative or use 10% 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) occur

Literature:

1. Fan X et al. NUDT15 polymorphism confer increased susceptibility to thiopurine-induced leukopenia in patients with autoimmune hepatitis and related cirrhosis. Front Pharmacol 2019;10:346.
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16. Ansari A et al. Influence of xanthine oxidase on thiopurine metabolism in Crohn's disease. Aliment Pharmacol Ther 2008;28:749-57.
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18. Kurzawski M et al. The impact of thiopurine s-methyltransferase polymorphism on azathioprine-induced myelotoxicity in renal transplant recipients. Ther Drug Monit 2005;27:435-41.
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30. McLeod HL et al. Analysis of thiopurine methyltransferase variant alleles in childhood acute lymphoblastic leukaemia. Br J Haematol 1999;105:696-700.
31. Andersen JB et al. Pharmacokinetics, dose adjustments, and 6-mercaptopurine/methotrexate drug interactions in two patients with thiopurine methyltransferase deficiency. Acta Paediatr 1998;87:108-11.
32. SmPC's Imuran (NL en VS), Puri-Nethol (NL) en Purixan (VS).

Date 17-09-2019

CYP2D6 IM: bisoprolol **2457**

This is NOT a gene-drug interaction.

Literature:

1. Nozawa T et al. Influence of CYP2D6 genotype on metoprolol plasma concentration and beta-adrenergic inhibition during long-term treatment: a comparison with bisoprolol. J Cardiovasc Pharmacol 2005;46:713-20.
2. Taguchi M et al. Pharmacokinetic variability of routinely administered bisoprolol in middle-aged and elderly Japanese patients. Biol Pharm Bull 2005;28:876-81.

Date 26-05-2009

CYP2D6 PM: bisoprolol **2456**

This is NOT a gene-drug interaction.

Literature:

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

Date 26-05-2009

CYP2D6 UM: bisoprolol **2458**

This is NOT a gene-drug interaction.

Literature:
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Date 26-05-2009

CYP2D6 IM: brexpiprazol **7046**

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:

1. Ishigooka J et al. Pharmacokinetics and safety of brexpiprazole following multiple-dose administration to Japanese patients with schizophrenia. J Clin Pharmacol 2018;58:74-80.
2. EPAR Rxulti.

Date 13-05-2019

CYP2D6 PM: brexpiprazol **7047**

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 Rxulti en SmPC Rexulti (VS).

Date 13-05-2019

CYP2D6 UM: brexpiprazol **7048**

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 Rxulti.

Date 13-05-2019

CYP2D6 IM: carvedilol **2345**

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.

Literature:

1. Shihmanter R et al. Variation in the CYP2D6 genotype is not associated with carvedilol dose changes in patients with heart failure. J Clin Pharm Ther 2014;39:432-8.
2. Nikolic VN et al. Population pharmacokinetics of carvedilol in patients with congestive heart failure. J Pharm Sci 2013;102:2851-8.
3. Sehrt D et al. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 2011;12:783-95.
4. Saito M et al. Population pharmacokinetics of R- and S-carvedilol in Japanese patients with chronic heart failure. Biol Pharm Bull 2010;33:1378-84.
5. Baudhuin LM et al. Relation of ADRB1, CYP2D6, and UGT1A1 polymorphisms with dose of, and response to, carvedilol or metoprolol therapy in patients with chronic heart failure. Am J Cardiol 2010;106:402-8.
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7. Takekuma Y et al. Evaluation of effects of polymorphism for metabolic enzymes on pharmacokinetics of carvedilol by population pharmacokinetic analysis. Biol Pharm Bull 2007;30:537-42.
8. Honda M et al. Multiple regression analysis of pharmacogenetic variability of carvedilol disposition in 54 healthy Japanese volunteers. Biol Pharm Bull 2006;29:772-8.
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10. Honda M et al. Effect of CYP2D6*10 on the pharmacokinetics of R- and S-carvedilol in healthy Japanese volunteers. Biol Pharm Bull 2005;28:1476-9.

Date 24-08-2016

CYP2D6 PM: carvedilol **2344**

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.

Literature:

1. Shihmanter R et al. Variation in the CYP2D6 genotype is not associated with carvedilol dose changes in patients with heart failure. J Clin Pharm Ther 2014;39:432-8.
2. Sehrt D et al. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 2011;12:783-95.
3. Baudhuin LM et al. Relation of ADRB1, CYP2D6, and UGT1A1 polymorphisms with dose of, and response to, carvedilol or metoprolol therapy in patients with chronic heart failure. Am J Cardiol 2010;106:402-8.
4. Giessmann T et al. CYP2D6 genotype and induction of intestinal drug transporters by rifampin predict presystemic clearance of carvedilol in healthy subjects. Clin Pharmacol Ther 2004;75:213-22.
5. Zhou HH et al. Stereoselective disposition of carvedilol is determined by CYP2D6. Clin Pharmacol Ther 1995;57:518-24.
6. SPC's Carvedilol Sandoz (Nederland) en Coreg (VS).

Date 24-08-2016

CYP2D6 UM: carvedilol **2346**

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.

Literature:

1. Shihmanter R et al. Variation in the CYP2D6 genotype is not associated with carvedilol dose changes in patients with heart failure. J Clin Pharm Ther 2014;39:432-8.
2. Sehrt D et al. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 2011;12:783-95.
3. Baudhuin LM et al. Relation of ADRB1, CYP2D6, and UGT1A1 polymorphisms with dose of, and response to, carvedilol or metoprolol therapy in patients with chronic heart failure. Am J Cardiol 2010;106:402-8.

Date 24-08-2016

CYP2C19 IM: citalopram **4195**

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:

1. Kumar Y et al. CYP2C19 variation, not citalopram dose nor serum level, is associated with QTc prolongation. J Psychopharmacol 2014;28:1143-8.
2. Chen B et al. Estimation of CYP2D6*10 genotypes on citalopram disposition in Chinese subjects by population pharmacokinetic assay. J Clin Pharm Ther 2013;38:504-11.
3. De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
4. Mrazek DA et al. CYP2C19 variation and citalopram response. Pharmacogenet Genomics 2011;2:1-9.
5. Fudio S et al. Evaluation of the influence of sex and CYP2C19 and CYP2D6 polymorphisms in the disposition of citalopram. Eur J Pharmacol 2010;25:200-4.
6. Hilli J et al. MAO-A and COMT genotypes as possible regulators of perinatal serotonergic symptoms after in utero exposure to SSRIs. Eur Neuropsychopharmacol 2009;19:363-70.
7. Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS ONE 2008;3:e1872.
8. Yin OQ et al. Phenotype-genotype relationship and clinical effects of citalopram in Chinese patients. J Clin Psychopharmacol 2006;26:367-72.
9. Rudberg I et al. Heterozygous mutation in CYP2C19 significantly increases the concentrations/dose ratio of racemic citalopram and escitalopram (S-citalopram). Ther Drug Monitor 2006;28:102-5.
10. Yu BN et al. Pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19. Drug Metab Dispos 2003;31:1255-9.
11. Jimmink A et al. Clinical toxicology of citalopram after acute intoxication with the sole drug or in combination with other drugs: overview of 26 cases. Ther Drug Monit 2008;30:365-71.

Date 14-05-2018

CYP2C19 PM: citalopram **4196**

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:

1. Kumar Y et al. CYP2C19 variation, not citalopram dose nor serum level, is associated with QTc prolongation. J Psychopharmacol 2014;28:1143-8.
2. De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
3. Mrazek DA et al. CYP2C19 variation and citalopram response. Pharmacogenet Genomics 2011;2:1-9.
4. Fudio S et al. Evaluation of the influence of sex and CYP2C19 and CYP2D6 polymorphisms in the disposition of citalopram. Eur J Pharmacol 2010;25:200-4.
5. Hilli J et al. MAO-A and COMT genotypes as possible regulators of perinatal serotonergic symptoms after in utero exposure to SSRIs. Eur Neuropsychopharmacol 2009;19:363-70.
6. Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS ONE 2008;3:e1872.
7. Yin OQ et al. Phenotype-genotype relationship and clinical effects of citalopram in Chinese patients. J Clin Psychopharmacol 2006;26:367-72.
8. Herrlin K et al. Metabolism of citalopram enantiomers in CYP2C19/CYP2D6 phenotyped panels of healthy Swedes. Br J Clin Pharmacol 2003;56:415-21.
9. Yu BN et al. Pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19. Drug Metab Dispos 2003;31:1255-9.
10. Baumann P et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol 1996;16:307-14.
11. Sindrup SH et al. Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. Ther Drug Monit 1993;15:11-7.
12. Jimmink A et al. Clinical toxicology of citalopram after acute intoxication with the sole drug or in combination with other drugs: overview of 26 cases. Ther Drug Monit 2008;30:365-71.
13. SPC's Cipramil en Celexa (VS).

Date 14-05-2018

CYP2C19 UM: citalopram **4197**

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:

1. De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
2. Mrazek DA et al. CYP2C19 variation and citalopram response. Pharmacogenet Genomics 2011;2:1-9.
3. Hilli J et al. MAO-A and COMT genotypes as possible regulators of perinatal serotonergic symptoms after in utero exposure to SSRIs. Eur Neuropsychopharmacol 2009;19:363-70.
4. Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS ONE 2008;3:e1872.
5. Jimmink A et al. Clinical toxicology of citalopram after acute intoxication with the sole drug or in combination with other drugs: overview of 26 cases. Ther Drug Monit 2008;30:365-71.

Date 14-05-2018

CYP2D6 IM: citalopram/escitalopram **1999**

This is NOT a gene-drug interaction.

Literature:

1. Chen B et al. Estimation of CYP2D6*10 genotypes on citalopram disposition in Chinese subjects by population pharmacokinetic assay. J Clin Pharm Ther 2013;38:504-11. PubMed PMID: 23981149.
2. Han KM et al. CYP2D6 P34S polymorphism and outcomes of escitalopram treatment in Koreans with major depression. Psychiatry Investig 2013;10:286-93. PubMed PMID: 24302953.
3. Huezo-Diaz P et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. J Psychopharmacol 2012;26:398-407. PubMed PMID: 21926427.
4. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67. PubMed PMID: 20531370.
5. Mrazek DA et al. CYP2C19 variation and citalopram response. Pharmacogenet Genomics 2011;21:1-9. PubMed PMID: 21192344.
6. Tsai MH et al. Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. Pharmacogenomics 2010;11:537-46. PubMed PMID: 20350136.
7. Fudio S et al. Evaluation of the influence of sex and CYP2C19 and CYP2D6 polymorphisms in the disposition of citalopram. Eur J Pharmacol 2010;626:200-4. PubMed PMID: 19840783.
8. Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS One 2008;3:e1872. PubMed PMID: 18382661.
9. Carlsson B et al. Enantioselective analysis of citalopram and metabolites in adolescents. Ther Drug Monit 2001;23:658-64.
10. SPC Cipramil.

Date 14-05-2018

CYP2D6 PM: citalopram/escitalopram **1998**

This is NOT a gene-drug interaction.

Literature:

1. Huezo-Diaz P et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. J Psychopharmacol 2012;26:398-407. PubMed PMID: 21926427.
2. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67. PubMed PMID: 20531370.
3. Mrazek DA et al. CYP2C19 variation and citalopram response. Pharmacogenet Genomics 2011;21:1-9. PubMed PMID: 21192344.
4. Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS One 2008;3:e1872. PubMed PMID: 18382661.
5. Grasmader K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.
6. Herrlin K et al. Metabolism of citalopram enantiomers in CYP2C19/CYP2D6 phenotyped panels of healthy Swedes. Br J Clin Pharmacol 2003;56:415-21.
7. Bondolfi G et al. Non-response to citalopram in depressive patients: pharmacokinetic and clinical consequences of a fluvoxamine augmentation. Psychopharmacology 1996;128:421-5.
8. Sindrup SH et al. Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. Ther Drug Monit 1993;15:11-7.
9. SPC's Cipramil, Lexapro (NL en VS) en Celexa (VS).

Date 14-05-2018

CYP2D6 UM: citalopram/escitalopram **2000**

This is NOT a gene-drug interaction.

Literature:

1. Huezo-Diaz P et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. J Psychopharmacol 2012;26:398-407. PubMed PMID: 21926427.
2. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67. PubMed PMID: 20531370.
3. Mrazek DA et al. CYP2C19 variation and citalopram response. Pharmacogenet Genomics 2011;21:1-9. PubMed PMID: 21192344.
4. Carlsson B et al. Enantioselective analysis of citalopram and metabolites in adolescents. Ther Drug Monit 2001;23:658-64.
5. SPC Cipramil.

Date 14-05-2018

CYP2C19 IM: clomipramine **7027**

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:

1. De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
2. Yokono A et al. The effect of CYP2C19 and CYP2D6 genotypes on the metabolism of clomipramine in Japanese psychiatric patients. J Clin Psychopharmacol 2001; 21:549-55.

Date 04-03-2019

CYP2C19 PM: clomipramine **7028**

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:

1. De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
2. Yokono A et al. The effect of CYP2C19 and CYP2D6 genotypes on the metabolism of clomipramine in Japanese psychiatric patients. J Clin Psychopharmacol 2001; 21:549-55.
3. Nielsen KK et al. Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. Clin Pharmacol Ther 1994;55:518-27.

Date 04-03-2019

CYP2C19 UM: clomipramine **7029**

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

- Indication OBSESSIVE COMPULSIVE DISORDER or ANXIETY DISORDERS:
  - avoid clomipramine
    Antidepressants that are not metabolised by CYP2C19 - or to a lesser extent - include, for example, fluoxetine, fluvoxamine and paroxetine.
  - if it is not possible to avoid clomipramine:
    - 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:

1. De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.

Date 04-03-2019

CYP2D6 IM: clomipramine **1481**

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/mLFor 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:

1. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
2. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67, persoonlijke communicatie.
3. Vandel P et al. Clomipramine, fluoxetine and CYP2D6 metabolic capacity in depressed patients. Hum Psychopharmacol 2004;19:293-8.
4. Yokono A et al. The effect of CYP2C19 and CYP2D6 genotypes on the metabolism of clomipramine in Japanese psychiatric patients. Clin Psychopharmacol 2001;21:549-55.
5. Balant-Gorgia et al. High blood concentrations of imipramine or clomipramine and therapeutic failure: a case report study using drug monitoring data. Ther Drug Monit 1989;11:415-20.

Date 19-11-2018

CYP2D6 IM: clomipramine **1481**

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/mLFor 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:

1. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
2. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67, persoonlijke communicatie.
3. Vandel P et al. Clomipramine, fluoxetine and CYP2D6 metabolic capacity in depressed patients. Hum Psychopharmacol 2004;19:293-8.
4. Yokono A et al. The effect of CYP2C19 and CYP2D6 genotypes on the metabolism of clomipramine in Japanese psychiatric patients. Clin Psychopharmacol 2001;21:549-55.
5. Balant-Gorgia et al. High blood concentrations of imipramine or clomipramine and therapeutic failure: a case report study using drug monitoring data. Ther Drug Monit 1989;11:415-20.

Date 19-11-2018

CYP2D6 PM: clomipramine **1480**

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:

1. de Jong C et al. Clomipramine toxicity in a CYP 2D6 poor metabolizer patient who suddenly stopped smoking. J Clin Psychopharmacol 2018;38:389-391.
2. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
3. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67, persoonlijke communicatie.
4. Stephan PL et al. Adverse drug reactions following nonresponse in a depressed patient with CYP2D6 deficiency and low CYP 3A4/5 activity. Pharmacopsychiatry 2006;39:150-2.
5. Danish University Antidepressant Group. Clomipramine dose-effect study in patients with depression: clinical end points and pharmacokinetics. Clin Pharmacol Ther 1999;66:152-65.
6. Nielsen KK et al. Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. Clin Pharmacol Ther 1994;55:518-27.
7. Tacke U et al. Debrisoquine hydroxylation phenotypes of patients with high versus low to normal serum antidepressant concentrations. J Clin Psychopharmacol 1992;12:262-7.
8. Nielsen KK et al. Steady-state plasma levels of clomipramine and its metabolites: impact of the sparteine/debrisoquine oxidation polymorphism. Eur J Clin Pharmacol 1992;43:405-11.
9. Balant-Gorgia AE et al. High plasma concentrations of desmethylclomipramine after chronic administration of clomipramine to a poor metabolizer. Eur J Clin Pharmacol 1987;32:101-2.
10. Balant-Gorgia AE et al. High blood concentrations of imipramine or clomipramine and therapeutic failure: a case report study using drug monitoring data. Ther Drug Monit 1989;11:415-20.
11. SmPC Anafranil (VS).

Date 19-11-2018

CYP2D6 UM: clomipramine **1482**

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

- use 1.5 times the standard dose and monitor the effect and side effects of the plasma concentrations of clomipramine and 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 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.
- if a dose increase is not wanted due to potential cardiotoxic hydroxy metabolites: avoid clomipramine.
  Antidepressants that are not metabolised by CYP2D6, or to a lesser extent, include citalopram and sertraline.

Literature:

1. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67.
2. de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67, persoonlijke communicatie.
3. Baumann P et al. Ultrarapid metabolism of clomipramine in a therapy-resistant depressive patient, as confirmed by CYP2 D6 genotyping. Pharmacopsychiatry 1998;31:72.
4. Bertilsson L et al. Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine. Lancet 1993;341:63.

Date 19-11-2018

CYP2D6 IM: clonidine **2531**

This is NOT a gene-drug interaction.

Literature:
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Date 24-08-2016

CYP2D6 PM: clonidine **2530**

This is NOT a gene-drug interaction.

Literature:
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Date 24-08-2016

CYP2D6 UM: clonidine **2532**

This is NOT a gene-drug interaction.

Literature:
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Date 24-08-2016

CYP2C19 IM: clopidogrel **2549**

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

- PERCUTANEOUS CORONARY INTERVENTION, STROKE or TIA:
  - choose an alternative or double the dose to 150 mg/day (600 mg loading dose)
    Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent).
- OTHER INDICATIONS:
  - no action required

Literature:

1. Lee J et al. CYP2C19 polymorphism is associated with amputation rates in patients taking clopidogrel after endovascular intervention for critical limb ischaemia. Eur J Vasc Endovasc Surg 2019;58:373-82.
2. Lan H et al. Anti-platelet therapy in mild cerebral infarction patients on the basis of CYP2C19 metabolizer status. Cell Transplant 2019;28:1039-44.
3. Kheiri B et al. CYP2C19 pharmacogenetics versus standard of care dosing for selecting antiplatelet therapy in patients with coronary artery disease: a meta-analysis of randomized clinical trials. Catheter Cardiovasc Interv 2019;93:1246-52.
4. Williams AK et al. CYP2C19 genotype-guided antiplatelet therapy and 30-day outcomes after percutaneous coronary intervention. Circ Genom Precis Med 2019;12:e002441.
5. Lee CR et al. Clinical outcomes and sustainability of using CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. Circ Genom Precis Med 2018;11:e002069.
6. Zhong Z et al. Effect of cytochrome P450 2C19 polymorphism on adverse cardiovascular events after drug-eluting stent implantation in a large Hakka population with acute coronary syndrome receiving clopidogrel in southern China. Eur J Clin Pharmacol 2018;74:423-31.
7. Wu Y et al. Impact of CYP2C19 polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE substudy. Pharmacogenomics J 2018;18:713-20.
8. Cavallari LH et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. JACC Cardiovasc Interv 2018;11:181-91.
9. Lin Y et al. Impact of glycemic control on efficacy of clopidogrel in transient ischemic attack or minor stroke patients with CYP2C19 genetic variants. Stroke 2017;48:998-1004.
10. Pan Y et al. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Circulation 2017;135:21-33.
11. Wang Y et al. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. JAMA 2016;316:70-8.
12. Ogawa H et al. Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study.
13. Shen DL et al. Clinical value of CYP2C19 genetic testing for guiding the antiplatelet therapy in a Chinese population. J Cardiovasc Pharmacol 2016;67:232-6.
14. Niu X et al. CYP2C19 polymorphism and clinical outcomes among patients of different races treated with clopidogrel: a systematic review and meta-analysis. J Huazhong Univ Sci Technolog Med Sci 2015;35:147-56.
15. Sorich MJ et al. CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta-analysis. Circ Cardiovasc Genet 2014;7:895-902.
16. Mao L et al. Cytochrome CYP2C19 polymorphism and risk of adverse clinical events in clopidogrel-treated patients: a meta-analysis based on 23,035 subjects. Arch Cardiovasc Dis 2013;106:517-27.
17. Xie X et al. Personalized antiplatelet therapy according to CYP2C19 genotype after percutaneous coronary intervention: a randomized control trial. Int J Cardiol 2013;168:3736-40.
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41. Fontana P et al. Biological effect of increased maintenance dose of clopidogrel in cardiovascular outpatients and influence of the cytochrome P450 2C19*2 allele on clopidogrel responsiveness. Thromb Res 2008;121:463-8.
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Date 23-12-2019

CYP2C19 PM: clopidogrel **2548**

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

- PERCUTANEOUS CORONARY INTERVENTION, STROKE or TIA:
  - avoid clopidogrel
    Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent).
- OTHER INDICATIONS:
  - determine the level of inhibition of platelet aggregation by clopidogrel
  - consider an alternative in poor responders
    Prasugrel and ticagrelor are not metabolised by CYP2C19 (or to a lesser extent).

Literature:

1. Lee J et al. CYP2C19 polymorphism is associated with amputation rates in patients taking clopidogrel after endovascular intervention for critical limb ischaemia. Eur J Vasc Endovasc Surg 2019;58:373-82.
2. Lan H et al. Anti-platelet therapy in mild cerebral infarction patients on the basis of CYP2C19 metabolizer status. Cell Transplant 2019;28:1039-44.
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18. Mao L et al. Cytochrome CYP2C19 polymorphism and risk of adverse clinical events in clopidogrel-treated patients: a meta-analysis based on 23,035 subjects. Arch Cardiovasc Dis 2013;106:517-27.
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21. Holmes MV et al. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA 2011;306:2704-14.
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23. Mega JL et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. JAMA 2011;306:2221-8.
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28. Aleil B et al. CYP2C19*2 polymorphism is not the sole determinant of the response to clopidogrel: implications for its monitoring. J Thromb Haemost 2009;7:1747-9.
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32. Giusti B et al. Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. Am J Cardiol 2009;103:806-11.
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34. Mega JL et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-62.
35. Simon T et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360:363-75.
36. Geisler T et al. CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation. Pharmacogenomics 2008;9:1251-9.
37. Umemura K et al. The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects. J Thromb Haemost 2008;6:1439-41.
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41. Trenk D et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol 2008;51:1925-34.
42. Frere C et al. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. Am J Cardiol 2008;101:1088-93.
43. Fontana P et al. Biological effect of increased maintenance dose of clopidogrel in cardiovascular outpatients and influence of the cytochrome P450 2C19*2 allele on clopidogrel responsiveness. Thromb Res 2008;121:463-8.
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45. Brandt JT et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007;5:2429-36.
46. 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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48. CBO Conceptrichtlijn Diagnostiek, Preventie en Behandeling van Veneuze Trombo-embolie en Secundaire Preventie Arteriële Trombose, 2008. www.cbo.nl.

Date 23-12-2019

CYP2C19 UM: clopidogrel **2550**

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:

1. Liu YP et al. Association of genetic variants in CYP2C19 and adverse clinical outcomes after treatment with clopidogrel: an updated meta-analysis. Thromb Res 2011;128:593-4.
2. Li Y et al. The gain-of-function variant allele CYP2C19*17: a double-edged sword between thrombosis and bleeding in clopidogrel-treated patients. J Thromb Haemost 2012;10:199-206.
3. Simon T et al. Genetic polymorphisms and the impact of a higher clopidogrel dose regimen on active metabolite exposure and antiplatelet response in healthy subjects. Clin Pharmacol Ther 2011;90:287-95.
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6. Mega JL et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-62.
7. Simon T et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360:363-75.
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Date 23-12-2019

CYP2D6 IM: clozapine **1530**

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:

1. Lesche D et al. Impact of CYP1A2, CYP2C19, and CYP2D6 genotype- and phenoconversion-predicted enzyme activity on clozapine exposure and symptom severity. Pharmacogenomics J 2020;20:192-201.
2. Tóth K et al. Potential role of patients' CYP3A-status in clozapine pharmacokinetics. Int J Neuropsychopharmacol 2017;20:529-37.
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4. Xu Q et al. Association studies of genomic variants with treatment response to risperidone, clozapine, quetiapine and chlorpromazine in the Chinese Han population. Pharmacogenomics J 2016;16:357-65.
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7. Melkersson KI et al. Impact of CYP1A2 and CYP2D6 polymorphisms on drug metabolism and on insulin and lipid elevations and insulin resistance in clozapine-treated patients. J Clin Psychiatry 2007;68:697-704.
8. Dettling M et al. Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. Psychopharmacology 2000;152:80-86.

Date 14-09-2020

CYP2D6 PM: clozapine **1529**

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:

1. Lesche D et al. Impact of CYP1A2, CYP2C19, and CYP2D6 genotype- and phenoconversion-predicted enzyme activity on clozapine exposure and symptom severity. Pharmacogenomics J 2020;20:192-201.
2. Tóth K et al. Potential role of patients' CYP3A-status in clozapine pharmacokinetics. Int J Neuropsychopharmacol 2017;20:529-37.
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Date 14-09-2020

CYP2D6 UM: clozapine **1531**

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:

1. Lesche D et al. Impact of CYP1A2, CYP2C19, and CYP2D6 genotype- and phenoconversion-predicted enzyme activity on clozapine exposure and symptom severity. Pharmacogenomics J 2020;20:192-201.
2. Tóth K et al. Potential role of patients' CYP3A-status in clozapine pharmacokinetics. Int J Neuropsychopharmacol 2017;20:529-37.
3. Jaquenoud Sirot E et al. ABCB1 and cytochrome P450 polymorphisms: clinical pharmacogenetics of clozapine. J Clin Psychopharmacol 2009;29:318-26.
4. Dettling M et al. Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. Psychopharmacology 2000;152:80-86.
5. Dettling M et al. Clozapine-induced agranulocytosis and hereditary polymorphisms of clozapine metabolizing enzymes: no association with myeloperoxidase and cytochrome P4502D6. Pharmacopsychiatry 2000;33:218-20

Date 14-09-2020

CYP2D6 IM: codeine **1584**

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:

1. Baber M et al. The pharmacogenetics of codeine pain relief in the postpartum period. Pharmacogenomics J 2015;15:430-5.
2. Prows CA et al. Codeine-related adverse drug reactions in children following tonsillectomy: a prospective study. Laryngoscope 2014;124:1242-50.
3. Kelly LE et al. A clinical tool for reducing central nervous system depression among neonates exposed to codeine through breast milk. PLoS One 2013;8:e70073.
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5. Williams DG et al. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. Br J Anaesth 2002;89:839-45.
6. Tseng CY et al. Formation of morphine from codeine in Chinese subjects of different CYP2D6 genotypes. Clin Pharmacol Ther 1996;60:177-82.
7. SPC Codeïnefosfaat Ratiopharm.

Date 20-11-2017

CYP2D6 PM: codeine **1583**

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. 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:

1. Baber M et al. The pharmacogenetics of codeine pain relief in the postpartum period. Pharmacogenomics J 2015;15:430-5.
2. Prows CA et al. Codeine-related adverse drug reactions in children following tonsillectomy: a prospective study. Laryngoscope 2014;124:1242-50.
3. Kelly LE et al. A clinical tool for reducing central nervous system depression among neonates exposed to codeine through breast milk. PLoS One 2013;8:e70073.
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5. VanderVaart S et al. CYP2D6 polymorphisms and codeine analgesia in postpartum pain management: a pilot study. Ther Drug Monit 2011;33:425-32.
6. Kirchheiner J et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J 2007;7:257-65.
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11. Hasselstrom J et al. The effect of codeine on gastrointestinal transit in extensive and poor metabolisers of debrisoquine. Eur J Clin Pharmacol 1997;53:145-8.
12. Poulsen L et al. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. Eur J Clin Pharmacol 1996;51:289-95.
13. Persson K et al. Patient-controlled analgesia (PCA) with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. Br J Clin Pharmacol 1995;39:182-6.
14. Yue QY et al. Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. Br J Clin Pharmacol 1991;31:635-42.
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16. Sindrup SH et al. Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. Clin Pharmacol Ther 1990;48:686-93.
17. SPC Codeïnefosfaat Ratiopharm.

Date 20-11-2017

CYP2D6 UM: codeine **1585**

The genetic variation increases the conversion of codeine to morphine. This can result in an increase in side effects. Death has occurred in children who received analgesic doses. One adult with reduced kidney function and co-medication with two CYP3A4 inhibitors became comatose after use of codeine for a cough.

Recommendation:

- DOSES HIGHER THAN 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND/OR ADDITIONAL RISK FACTORS, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:
  Codeine is contra-indicated
  - if possible, select an alternative
    - For PAIN: do not select tramadol, as this is also metabolised by CYP2D6.
      Morphine is not metabolised by CYP2D6. Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.
    - For COUGH: noscapine is not metabolised by CYP2D6.
- DOSES LOWER THAN OR EQUAL TO 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND NO ADDITIONAL RISK FACTORS, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:
  - no action required

Literature:

1. Baber M et al. The pharmacogenetics of codeine pain relief in the postpartum period. Pharmacogenomics J 2015;15:430-5.
2. Ray JG et al. Risk of overdose and death following codeine prescription among immigrants. J Epidemiol Community Health 2014;68:1057-63.
3. Prows CA et al. Codeine-related adverse drug reactions in children following tonsillectomy: a prospective study. Laryngoscope 2014;124:1242-50.
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5. Kelly LE et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012;129:e1343-7.
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8. Ciszkowski C et al. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med 2009;361:827-8.
9. Madadi P et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. Clin Pharmacol Ther 2009;85:31-5.
10. Koren G et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006;368:704.
11. Kirchheiner J et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J 2007;7:257-65.
12. Gasche Y et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004;351:2827-31.
13. Dalen P et al. Quick onset of severe abdominal pain after codeine in an ultrarapid metabolizer of debrisoquine. Ther Drug Monit 1997;19:543-4.
14. European Medicines Agency. Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation. 28-06-13.
15. SPC Codeïnefosfaat Ratiopharm.
16. SPC Codeine Sulfate Tablets (VS).

Date 20-11-2017

CYP2D6 IM: disopyramide **2537**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2D6 PM: disopyramide **2536**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2D6 UM: disopyramide **2538**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2C19 IM: doxepine **7021**

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:

1. Kirchheiner J et al. Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. Pharmacogenetics 2002;12:571-80.

Date 04-03-2019

CYP2C19 PM: doxepine **7022**

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:

1. Kirchheiner J et al. Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. Pharmacogenetics 2002;12:571-80.
2. SmPC Silenor (VS).

Date 04-03-2019

CYP2C19 UM: doxepine **7023**

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:

1. Kirchheiner J et al. Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. Pharmacogenetics 2002;12:571-80.

Date 04-03-2019

CYP2D6 IM: doxepine **2015**

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

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

Literature:

1. Kirchheiner J et al. Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. Pharmacogenetics 2002;12:571-80.

Date 19-11-2018

CYP2D6 PM: doxepine **2016**

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

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

Literature:

1. Koski A et al. A fatal doxepin poisoning associated with a defective CYP2D6 genotype. Am J Forensic Med Pathol 2007;28:259-61.
2. Kirchheiner J et al. Impact of the CYP2D6 ultra-rapid metabolizer genotype on doxepin pharmacokinetics and serotonin in platelets. Pharmacogenet Genomics 2005;15:579-87.
3. Grasmader K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.
4. Kirchheiner J et al. Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. Pharmacogenetics 2002;12:571-80.
5. Tacke U et al. Debrisoquine hydroxylation phenotypes of patients with high versus low to normal serum antidepressant concentrations. J Clin Psychopharmacol 1992;12:262-7.
6. SmPC Silenor (VS).

Date 19-11-2018

CYP2D6 UM: doxepine **2017**

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

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

Literature:

1. Kirchheiner J et al. Impact of the CYP2D6 ultra-rapid metabolizer genotype on doxepin pharmacokinetics and serotonin in platelets. Pharmacogenet Genomics 2005;15:579-87.

Date 19-11-2018

CYP2D6 IM: duloxetine **1673**

This is NOT a gene-drug interaction.

Literature:

1. Kamei S et al. Rapid onset of syndrome of inappropriate antidiuretic hormone secretion induced by duloxetine in an elderly type 2 diabetic patient with painful diabetic neuropathy. J Diabetes Investig 2015;6:343-5.
2. Lobo ED et al. Pharmacokinetics of orally administered duloxetine in children and adolescents with major depressive disorder. Clin Pharmacokinet 2014;53:731-40.
3. Beatty NC et al. Pharmacogenetic workup of perioperative serotonin syndrome. J Clin Anesth 2013;25:662-5.
4. Tianmei S et al. Pharmacokinetics and tolerability of duloxetine following oral administration to healthy Chinese subjects. Clin Pharmacokinet 2007;46:767-75.

Date 30-01-2017

CYP2D6 PM: duloxetine **1674**

This is NOT a gene-drug interaction.

Literature:

1. Lobo ED et al. Pharmacokinetics of orally administered duloxetine in children and adolescents with major depressive disorder. Clin Pharmacokinet 2014;53:731-40.
2. Chan C et al. Duloxetine pharmacokinetics are similar in Japanese and Caucasian subjects. Br J Clin Pharmacol 2007;63:310-4.
3. SPC Cymbalta.

Date 30-01-2017

CYP2D6 UM: duloxetine **1675**

This is NOT a gene-drug interaction.

Literature:

1. Lobo ED et al. Pharmacokinetics of orally administered duloxetine in children and adolescents with major depressive disorder. Clin Pharmacokinet 2014;53:731-40.

Date 30-01-2017

CYP2B6 *1/*5: efavirenz **6928**

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:

1. Burger D et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J Clin Pharmacol 2006;61:148-54.

Date 05-03-2018

CYP2B6 *5/*5: efavirenz **6929**

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:

1. Burger D et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J Clin Pharmacol 2006;61:148-54.

Date 05-03-2018

CYP2B6 *5/*6 of *5/*18: efavirenz **6930**

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

Recommendation:

- Determine the efavirenz plasma concentration if side effects occur and reduce the dose if needed.
  In 14 adults with a genotype with the same effect, a reduction of the dose to 400 mg/day (2/3 of the standard dose) was sufficient to achieve therapeutic plasma concentrations and for the side effects to reduce or disappear.
  The therapeutic range established for efavirenz is 1000-4000 ng/mL.

Literature:

1. Vujkovic M et al. CYP2B6 516G>T minor allele protective of late virologic failure in efavirenz-treated HIV-infected patients in Botswana. J Acquir Immune Defic Syndr 2017 May 5 [Epub ahead of print].
2. Leger P et al. Pharmacogenetics of efavirenz discontinuation for reported central nervous system symptoms appears to differ by race. Pharmacogenet Genomics 2016;26:473-80.
3. Cusato J et al. Efavirenz pharmacogenetics in a cohort of Italian patients. Int J Antimicrob Agents 2016;47:117-23.
4. Dickinson L et al. Comprehensive pharmacokinetic, pharmacodynamic and pharmacogenetic evaluation of once-daily efavirenz 400 and 600 mg in treatment-naïve HIV-infected patients at 96 weeks: results of the ENCORE1 study. Clin Pharmacokinet 2016;55:861-73.
5. Swart M et al. An expanded analysis of pharmacogenetics determinants of efavirenz response that includes 3'-UTR single nucleotide polymorphisms among black South African HIV/AIDS patients. Front Genet 2016;6:356.
6. Meng X et al. Effect of CYP2B6 gene polymorphisms on efavirenz plasma concentrations in Chinese patients with HIV infection. PLoS One 2015;10:e0130583.
7. Haas DW et al. Functional CYP2B6 variants and virologic response to an efavirenz-containing regimen in Port-au-Prince, Haiti. J Antimicrob Chemother 2014;69:2187-90.
8. Martín AS et al. Dose reduction of efavirenz: an observational study describing cost-effectiveness, pharmacokinetics and pharmacogenetics. Pharmacogenomics 2014;15:997-1006.
9. Bertrand J et al. Dependence of efavirenz- and rifampicin-isoniazid-based antituberculosis treatment drug-drug interaction on CYP2B6 and NAT2 genetic polymorphisms: ANRS 12154 study in Cambodia. J Infect Dis 2014;209:399-408.
10. Sarfo FS et al. Pharmacogenetic associations with plasma efavirenz concentrations and clinical correlates in a retrospective cohort of Ghanaian HIV-infected patients. J Antimicrob Chemother 2014;69:491-9. PubMed PMID: 24080498.
11. Ngaimisi E et al. Importance of ethnicity, CYP2B6 and ABCB1 genotype for efavirenz pharmacokinetics and treatment outcomes: a parallel-group prospective cohort study in two sub-Saharan Africa populations. PLoS One 2013;8:e67946. PubMed PMID: 23861838.
12. Yimer G et al. High plasma efavirenz level and CYP2B6*6 are associated with efavirenz-based HAART-induced liver injury in the treatment of naïve HIV patients from Ethiopia: a prospective cohort study. Pharmacogenomics J 2012;12:499-506. PubMed PMID: 21862974.
13. Mugusi S et al. Liver enzyme abnormalities and associated risk factors in HIV patients on efavirenz-based HAART with or without tuberculosis co-infection in Tanzania. PLoS One 2012;7:e40180. PubMed PMID: 22808112.
14. Wyen C et al. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. J Antimicrob Chemother 2011;66:2092-8. PubMed PMID: 21715435.
15. Carr DF et al. Haplotype structure of CYP2B6 and association with plasma efavirenz concentrations in a Chilean HIV cohort. J Antimicrob Chemother 2010;65:1889-93. PubMed PMID: 20639527.
16. Gatanaga H et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6*6 and* 26. Clin Infect Dis 2007;45:1230-7. PubMed PMID: 17918089.
17. Burger D et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J Clin Pharmacol 2006;61:148-54.
18. Haas DW et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir: an Adult Aids Clinical Trials Group study. J Infect Dis 2005;192:1931-42. PubMed PMID: 16267764.

Date 05-03-2018

CYP2B6 IM: efavirenz **4754**

Genetic variations increase the efavirenz plasma concentration and therefore the risk of side effects. However, the efavirenz plasma concentration remains within the therapeutic range for the majority of patients.

Recommendation:

1. Determine the efavirenz plasma concentration if side effects occur and reduce the dose if needed.
   In 14 IM adults, a dose reduction to 400 mg/day (2/3rd of the standard dose) was sufficient to achieve therapeutic plasma concentrations and to reduce or resolve side effects.
   The therapeutic range established for efavirenz is 1000-4000 ng/ml.

Literature:

1. Vujkovic M et al. CYP2B6 516G>T minor allele protective of late virologic failure in efavirenz-treated HIV-infected patients in Botswana. J Acquir Immune Defic Syndr 2017 May 5 [Epub ahead of print].
2. Leger P et al. Pharmacogenetics of efavirenz discontinuation for reported central nervous system symptoms appears to differ by race. Pharmacogenet Genomics 2016;26:473-80.
3. Cusato J et al. Efavirenz pharmacogenetics in a cohort of Italian patients. Int J Antimicrob Agents 2016;47:117-23.
4. Dickinson L et al. Comprehensive pharmacokinetic, pharmacodynamic and pharmacogenetic evaluation of once-daily efavirenz 400 and 600 mg in treatment-naïve HIV-infected patients at 96 weeks: results of the ENCORE1 study. Clin Pharmacokinet 2016;55:861-73.
5. Swart M et al. An expanded analysis of pharmacogenetics determinants of efavirenz response that includes 3'-UTR single nucleotide polymorphisms among black South African HIV/AIDS patients. Front Genet 2016;6:356.
6. Meng X et al. Effect of CYP2B6 gene polymorphisms on efavirenz plasma concentrations in Chinese patients with HIV infection. PLoS One 2015;10:e0130583.
7. Haas DW et al. Functional CYP2B6 variants and virologic response to an efavirenz-containing regimen in Port-au-Prince, Haiti. J Antimicrob Chemother 2014;69:2187-90.
8. Martín AS et al. Dose reduction of efavirenz: an observational study describing cost-effectiveness, pharmacokinetics and pharmacogenetics. Pharmacogenomics 2014;15:997-1006.
9. Bertrand J et al. Dependence of efavirenz- and rifampicin-isoniazid-based antituberculosis treatment drug-drug interaction on CYP2B6 and NAT2 genetic polymorphisms: ANRS 12154 study in Cambodia. J Infect Dis 2014;209:399-408.
10. Sarfo FS et al. Pharmacogenetic associations with plasma efavirenz concentrations and clinical correlates in a retrospective cohort of Ghanaian HIV-infected patients. J Antimicrob Chemother 2014;69:491-9. PubMed PMID: 24080498.
11. Ngaimisi E et al. Importance of ethnicity, CYP2B6 and ABCB1 genotype for efavirenz pharmacokinetics and treatment outcomes: a parallel-group prospective cohort study in two sub-Saharan Africa populations. PLoS One 2013;8:e67946. PubMed PMID: 23861838.
12. Yimer G et al. High plasma efavirenz level and CYP2B6*6 are associated with efavirenz-based HAART-induced liver injury in the treatment of naïve HIV patients from Ethiopia: a prospective cohort study. Pharmacogenomics J 2012;12:499-506. PubMed PMID: 21862974.
13. Mugusi S et al. Liver enzyme abnormalities and associated risk factors in HIV patients on efavirenz-based HAART with or without tuberculosis co-infection in Tanzania. PLoS One 2012;7:e40180. PubMed PMID: 22808112.
14. Wyen C et al. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. J Antimicrob Chemother 2011;66:2092-8. PubMed PMID: 21715435.
15. Carr DF et al. Haplotype structure of CYP2B6 and association with plasma efavirenz concentrations in a Chilean HIV cohort. J Antimicrob Chemother 2010;65:1889-93. PubMed PMID: 20639527.
16. Gatanaga H et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6*6 and* 26. Clin Infect Dis 2007;45:1230-7. PubMed PMID: 17918089.
17. Haas DW et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir: an Adult Aids Clinical Trials Group study. J Infect Dis 2005;192:1931-42. PubMed PMID: 16267764.

Date 05-03-2018

CYP2B6 PM: efavirenz **4755**

Genetic variations increase the risk of side effects. The standard dose leads to an efavirenz concentration in the toxic range in the majority of patients with this genotype.

Recommendation:

- Efavirenz in MONOpreparation, adults and children FROM 40 KG:
  - Body mass index LESS THAN or EQUAL to 25:
    1. The recommended initial dose is 400 mg/day and this dose should be titrated to plasma concentration if needed (further reduction to 200 mg/day or in rare cases an increase to 600 mg/day).
       The therapeutic range established for efavirenz is 1000-4000 ng/ml.
  - Body mass index GREATER than 25:
    1. The recommended initial dose is 600 mg/day and this dose should be titrated to plasma concentration if needed (reduction to 400 or 200 mg/day).
       The therapeutic range established for efavirenz is 1000-4000 ng/ml.
- Efavirenz in MONOpreparation, children LIGHTER THAN 40 KG:
  1. Start with the standard dose and titrate this dose to plasma concentration if needed. In adults, therapeutic plasma concentrations were achieved at either 2/3rd of the standard dose (1/3rd of the patients) or 1/3rd of the standard dose (2/3rd of the patients). In children younger than 3 years, therapeutic plasma concentrations were achieved at doses of approximately 10 mg/kg per day (as capsules) (100 mg/day for 7-14 kg and 150 mg/day for 14-17 kg; 50-75% of the standard dose).

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

- Efavirenz in COMBINATION preparation:
  1. Initiate the combination preparation and titrate the efavirenz dose to plasma concentration if needed (reduction to 400 or 200 mg/day)
     The therapeutic range established for efavirenz is 1000-4000 ng/ml.

Note: 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 3 studies with low efavirenz plasma concentrations in EM patients (2 of the 3 studies performed in Africa and 1 study in the United States and Italy). A recent study showed a similar virological response for efavirenz 400 and 600 mg/day in patients not selected on genotype. The risk of underdose is therefore very small if the initial dose is reduced to 400 mg/day. Two small studies showed that dose reductions did not reduce the efficacy (HIV remained undetectable), but side effects did reduce in 24 PM patients.
Compliance improves with administration of a combination preparation and the absence of unnecessary side effects due to excessive plasma concentrations.
Consideration to CYP2B6 inducers such as rifampicin is not needed in PM patients. The significantly low or absent metabolic capacity of CYP2B6 makes induction of little to no relevance. Moreover, the effects of enzyme induction by rifampicin and enzyme inhibition by isoniazid on efavirenz plasma concentrations seem to largely cancel each other out, independent of the CYP2B6 phenotype of the patient.

Literature:

1. Vujkovic M et al. CYP2B6 516G>T minor allele protective of late virologic failure in efavirenz-treated HIV-infected patients in Botswana. J Acquir Immune Defic Syndr 2017 May 5 [Epub ahead of print].
2. Bolton Moore C et al. CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3-36 months with HIV infection. AIDS 2017;31:1129-1136.
3. Leger P et al. Pharmacogenetics of efavirenz discontinuation for reported central nervous system symptoms appears to differ by race. Pharmacogenet Genomics 2016;26:473-80.
4. Cusato J et al. Efavirenz pharmacogenetics in a cohort of Italian patients. Int J Antimicrob Agents 2016;47:117-23.
5. Dickinson L et al. Comprehensive pharmacokinetic, pharmacodynamic and pharmacogenetic evaluation of once-daily efavirenz 400 and 600 mg in treatment-naïve HIV-infected patients at 96 weeks: results of the ENCORE1 study. Clin Pharmacokinet 2016;55:861-73.
6. Swart M et al. An expanded analysis of pharmacogenetics determinants of efavirenz response that includes 3'-UTR single nucleotide polymorphisms among black South African HIV/AIDS patients. Front Genet 2016;6:356.
7. Meng X et al. Effect of CYP2B6 gene polymorphisms on efavirenz plasma concentrations in Chinese patients with HIV infection. PLoS One 2015;10:e0130583.
8. Haas DW et al. Functional CYP2B6 variants and virologic response to an efavirenz-containing regimen in Port-au-Prince, Haiti. J Antimicrob Chemother 2014;69:2187-90.
9. Martín AS et al. Dose reduction of efavirenz: an observational study describing cost-effectiveness, pharmacokinetics and pharmacogenetics. Pharmacogenomics 2014;15:997-1006.
10. Bertrand J et al. Dependence of efavirenz- and rifampicin-isoniazid-based antituberculosis treatment drug-drug interaction on CYP2B6 and NAT2 genetic polymorphisms: ANRS 12154 study in Cambodia. J Infect Dis 2014;209:399-408.
11. Sarfo FS et al. Pharmacogenetic associations with plasma efavirenz concentrations and clinical correlates in a retrospective cohort of Ghanaian HIV-infected patients. J Antimicrob Chemother 2014;69:491-9. PubMed PMID: 24080498.
12. Ngaimisi E et al. Importance of ethnicity, CYP2B6 and ABCB1 genotype for efavirenz pharmacokinetics and treatment outcomes: a parallel-group prospective cohort study in two sub-Saharan Africa populations. PLoS One 2013;8:e67946. PubMed PMID: 23861838.
13. Yimer G et al. High plasma efavirenz level and CYP2B6*6 are associated with efavirenz-based HAART-induced liver injury in the treatment of naïve HIV patients from Ethiopia: a prospective cohort study. Pharmacogenomics J 2012;12:499-506. PubMed PMID: 21862974.
14. Mugusi S et al. Liver enzyme abnormalities and associated risk factors in HIV patients on efavirenz-based HAART with or without tuberculosis co-infection in Tanzania. PLoS One 2012;7:e40180. PubMed PMID: 22808112.
15. Wyen C et al. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. J Antimicrob Chemother 2011;66:2092-8. PubMed PMID: 21715435.
16. Ribaudo HJ et al. Effect of CYP2B6, ABCB1, and CYP3A5 polymorphisms on efavirenz pharmacokinetics and treatment response: an AIDS Clinical Trials Group study. J Infect Dis 2010;202:717-22. PubMed PMID: 20662624.
17. Carr DF et al. Haplotype structure of CYP2B6 and association with plasma efavirenz concentrations in a Chilean HIV cohort. J Antimicrob Chemother 2010;65:1889-93. PubMed PMID: 20639527.
18. Gatanaga H et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. Clin Infect Dis 2007;45:1230-7. PubMed PMID: 17918089.
19. Haas DW et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir: an Adult Aids Clinical Trials Group study. J Infect Dis 2005;192:1931-42. PubMed PMID: 16267764.
20. SPC's Efavirenz Mylan en Sustiva (VS).
21. ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet 2014;383:1474-82.

Date 05-03-2018

CYP2D6 IM: eliglustat **6138**

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, aprepitant, 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
- 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):
  - choose an alternative if possible
  - if an alternative is not an option:
    - consider a dose of 84 mg eliglustat 1x daily
    - be alert to side effects
- Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine):
  1. choose an alternative
  2. if an alternative is not an option:
     1. 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, rifabutine, hypericum):
  Eliglustat is not recommended. The plasma concentration may decrease so sharply that a therapeutic effect cannot be achieved.
  1. choose an alternative if possible
- NO co-medication with a moderate or strong CYP2D6 or CYP3A inhibitor or strong CYP3A inducer:
  1. use the standard dose of 84 mg 2x daily

Literature:

1. SPC's Cerdelga (Nederland en VS).

Date 31-10-2016

CYP2D6 PM: eliglustat **6137**

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 ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir):
  Eliglustat is contra-indicated.
  1. choose an alternative if possible
- Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine):
  Eliglustat is not recommended.
  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 not recommended. The plasma concentration may decrease so sharply that a therapeutic effect cannot be achieved.
  1. choose an alternative if possible
- NO co-medication with a CYP3A inhibitor or strong CYP3A inducer:
  1. use a dose of 84 mg 1x daily

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

Date 31-10-2016

CYP2D6 UM: eliglustat **6139**

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

Recommendation:

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

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

Date 31-10-2016

CYP2C19 IM: escitalopram **1821**

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

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

Literature:

1. Tsuchimine S et al. Effects of cytochrome P450 (CYP) 2C19 genotypes on steady-state plasma concentrations of escitalopram and its desmethyl metabolite in Japanese patients with depression. Ther Drug Monit 2018 Mar 22 [Epub ahead of print].
2. Jukić MM et al. Impact of CYP2C19 genotype on escitalopram exposure and therapeutic failure: a retrospective study based on 2,087 patients. Am J Psychiatry 2018 Jan 12 [Epub ahead of print].
3. He Q et al. Correlation between cytochrome P450 2C19 genetic polymorphism and treatment response to escitalopram in panic disorder. Pharmacogenet Genomics 2017;27:279-284.
4. Bishop JR et al. Escitalopram pharmacogenetics: CYP2C19 relationships with dosing and clinical outcomes in autism spectrum disorder. Pharmacogenet Genomics 2015:548-54.
5. Hodgson K et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl) 2015;232: 2609-17.
6. Kumar Y et al. CYP2C19 variation, not citalopram dose nor serum level, is associated with QTc prolongation. J Psychopharmacol 2014;28:1143-8.
7. Waade RB et al. Impact of age on serum concentrations of venlafaxine and escitalopram in different CYP2D6 and CYP2C19 genotype subgroups. Eur J Clin Pharmacol 2014;70:933-40.
8. Hodgson K et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. J Psychopharmacol 2014;28:133-41.
9. Ng C et al. Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Hum Psychopharmacol 2013;28:516-22.
10. Huezo-Diaz et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. J Psychopharmacol 2012;26:398-407.
11. Brasch-Andersen C et al. A candidate gene study of serotonergic pathway genes and pain relief during treatment with escitalopram in patients with neuropathic pain shows significant association to serotonin receptor2C (HTR2C). Eur J Clin Pharmacol 2011; 67:1131-7.
12. Tsai et al. Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. Pharmacogenomics 2010:11;537-46.
13. Jin Y et al. Effect of age, weight, and CYP2C19 genotype on escitalopram exposure. J Clin Pharmacol. 2010;50:62-72.
14. Rudberg I et al. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther 2008;83:322-7.
15. Rudberg I et al. Heterozygous mutation in CYP2C19 significantly increases the concentrations/dose ratio of racemic citalopram and escitalopram (S-citalopram). Ther Drug Monitor 2006;28:102-5.

Date 14-05-2018

CYP2C19 PM: escitalopram **1822**

The risk of conversion 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 conversion to another antidepressant will be offset.

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

Literature:

1. Tsuchimine S et al. Effects of cytochrome P450 (CYP) 2C19 genotypes on steady-state plasma concentrations of escitalopram and its desmethyl metabolite in Japanese patients with depression. Ther Drug Monit 2018 Mar 22 [Epub ahead of print].
2. Jukić MM et al. Impact of CYP2C19 genotype on escitalopram exposure and therapeutic failure: a retrospective study based on 2,087 patients. Am J Psychiatry 2018 Jan 12 [Epub ahead of print].
3. He Q et al. Correlation between cytochrome P450 2C19 genetic polymorphism and treatment response to escitalopram in panic disorder. Pharmacogenet Genomics 2017;27:279-284.
4. Asakura S et al. Long-term administration of escitalopram in patients with social anxiety disorder in Japan. Neuropsychiatr Dis Treat 2016;12:1817-25.

5. Bishop JR et al. Escitalopram pharmacogenetics: CYP2C19 relationships with dosing and clinical outcomes in autism spectrum disorder. Pharmacogenet Genomics 2015:548-54.
6. Hodgson K et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl) 2015;232: 2609-17.
7. Kumar Y et al. CYP2C19 variation, not citalopram dose nor serum level, is associated with QTc prolongation. J Psychopharmacol 2014;28:1143-8.
8. Waade RB et al. Impact of age on serum concentrations of venlafaxine and escitalopram in different CYP2D6 and CYP2C19 genotype subgroups. Eur J Clin Pharmacol 2014;70:933-40.
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10. Ng C et al. Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Hum Psychopharmacol 2013;28:516-22.
11. Huezo-Diaz et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. J Psychopharmacol 2012;26:398-407.
12. Brasch-Andersen C et al. A candidate gene study of serotonergic pathway genes and pain relief during treatment with escitalopram in patients with neuropathic pain shows significant association to serotonin receptor2C (HTR2C). Eur J Clin Pharmacol 2011; 67:1131-7.
13. Tsai et al. Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. Pharmacogenomics 2010:11;537-46.
14. Noehr-Jensen et al. Impact of CYP2C19 phenotypes on escitalopram metabolism and an evaluation of pupillometry as a serotonergic biomarker. Eur J Clin Pharmacol 2009;65:887-94.
15. Jin Y et al. Effect of age, weight, and CYP2C19 genotype on escitalopram exposure. J Clin Pharmacol. 2010;50:62-72.
16. Rudberg I et al. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther 2008;83:322-7.
17. SPC's Lexapro (NL en VS).

Date 14-05-2018

CYP2C19 UM: escitalopram **1820**

The risk of conversion 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:

1. Jukić MM et al. Impact of CYP2C19 genotype on escitalopram exposure and therapeutic failure: a retrospective study based on 2,087 patients. Am J Psychiatry 2018 Jan 12 [Epub ahead of print].
2. Bishop JR et al. Escitalopram pharmacogenetics: CYP2C19 relationships with dosing and clinical outcomes in autism spectrum disorder. Pharmacogenet Genomics 2015:548-54.
3. Hodgson K et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl) 2015;232: 2609-17.
4. Hodgson K et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. J Psychopharmacol 2014;28:133-41.
5. Huezo-Diaz et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. J Psychopharmacol 2012;26:398-407.
6. Brasch-Andersen C et al. A candidate gene study of serotonergic pathway genes and pain relief during treatment with escitalopram in patients with neuropathic pain shows significant association to serotonin receptor2C (HTR2C). Eur J Clin Pharmacol 2011; 67:1131-7.
7. Jin Y et al. Effect of age, weight, and CYP2C19 genotype on escitalopram exposure. J Clin Pharmacol. 2010;50:62-72.
8. Ohlsson Rosenborg S et al. Kinetics of omeprazole and escitalopram in relation to the CYP2C19*17 allele in healthy subjects. Eur J Clin Pharmacol 2008 Jul 25. 4;1175-79.
9. Rudberg I et al. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther 2008;83:322-7.

Date 14-05-2018

CYP2C19 IM: esomeprazol **1824**

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:

1. Deshpande N et al. Rapid and ultra-rapid metabolizers with CYP2C19*17 polymorphism do not respond to standard therapy with proton pump inhibitors. Meta Gene 2016;9:159-64.
2. Hsu WH et al. Genetic polymorphisms of CYP2C19 and IL1B have no influence on esomeprazole treatment for mild erosive esophagitis. Kaohsiung J Med Sci 2015;31:255-9.
3. Tang HL et al. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. PLoS One 2013;8:e62162.
4. Lee VW et al. Pharmacogenetics of esomeprazole or rabeprazole-based triple therapy in Helicobacter pylori eradication in Hong Kong non-ulcer dyspepsia Chinese subjects. J Clin Pharm Ther 2010;35:343-50.
5. Hunfeld NG et al. A comparison of the acid-inhibitory effects of esomeprazole and pantoprazole in relation to pharmacokinetics and CYP2C19 polymorphism. Aliment Pharmacol Ther 2010;31:150-9.
6. Lou HY et al. Optimal dose regimens of esomeprazole for gastric acid suppression with minimal influence of the CYP2C19 polymorphism. Eur J Clin Pharmacol 2009;65:55-64.
7. Sheu BS et al. Body mass index can determine the healing of reflux esophagitis with Los Angeles Grades C and D by esomeprazole. Am J Gastroenterol 2008;103:2209-14.
8. Li ZS et al. Effect of esomeprazole and rabeprazole on intragastric pH in healthy Chinese: an open, randomized crossover trial. J Gastroenterol Hepatol 2007;22:815-20.
9. Schwab M et al. Esomeprazole-induced healing of gastroesophageal reflux disease is unrelated to the genotype of CYP2C19: evidence from clinical and pharmacokinetic data. Clin Pharmacol Ther 2005;78:627-34.
10. Kuo CH et al. Efficacy of levofloxacin-based rescue therapy for Helicobacter pylori infection after standard triple therapy: a randomized controlled trial. J Antimicrob Chemother 2009;63:1017-24.
11. Kang JM et al. Effect of the CYP2C19 polymorphism on the eradication rate of Helicobacter pylori infection by 7-day triple therapy with regular proton pump inhibitor dosage. J Gastroenterol Hepatol 2008;23:1287-91.
12. Miehlke S et al. One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradication of persistent Helicobacter pylori resistant to both metronidazole and clarithromycin. Helicobacter 2008;13:69-74.
13. Miehlke S et al. Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. Aliment Pharmacol Ther 2006;24:395-403.
14. Sheu BS et al. Esomeprazole 40 mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to CYP2C19 metabolism. Aliment Pharmacol Ther 2005;21:283-8.

Date 05-03-2018

CYP2C19 PM: esomeprazol **1825**

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:

1. Deshpande N et al. Rapid and ultra-rapid metabolizers with CYP2C19*17 polymorphism do not respond to standard therapy with proton pump inhibitors. Meta Gene 2016;9:159-64.
2. Hsu WH et al. Genetic polymorphisms of CYP2C19 and IL1B have no influence on esomeprazole treatment for mild erosive esophagitis. Kaohsiung J Med Sci 2015;31:255-9.
3. Tang HL et al. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. PLoS One 2013;8:e62162.
4. Lee VW et al. Pharmacogenetics of esomeprazole or rabeprazole-based triple therapy in Helicobacter pylori eradication in Hong Kong non-ulcer dyspepsia Chinese subjects. J Clin Pharm Ther 2010;35:343-50.
5. Lou HY et al. Optimal dose regimens of esomeprazole for gastric acid suppression with minimal influence of the CYP2C19 polymorphism. Eur J Clin Pharmacol 2009;65:55-64.
6. Sheu BS et al. Body mass index can determine the healing of reflux esophagitis with Los Angeles Grades C and D by esomeprazole. Am J Gastroenterol 2008;103:2209-14.
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8. Schwab M et al. Esomeprazole-induced healing of gastroesophageal reflux disease is unrelated to he genotype of CYP2C19: evidence from clinical and pharmacokinetic data. Clin Pharmacol Ther 2005;78:627-34.
9. Kuo CH et al. Efficacy of levofloxacin-based rescue therapy for Helicobacter pylori infection after standard triple therapy: a randomized controlled trial. J Antimicrob Chemother 2009;63:1017-24.
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11. Miehlke S et al. One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradication of persistent Helicobacter pylori resistant to both metronidazole and clarithromycin. Helicobacter 2008;13:69-74.
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2006;24:395-403.
13. Sheu BS et al. Esomeprazole 40 mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to CYP2C19 metabolism. Aliment Pharmacol Ther 2005;21:283-8.
14. SPC Nexium (Nederlands en Amerikaans).

Date 05-03-2018

CYP2C19 UM: esomeprazol **1826**

NO action is required for this gene-drug interaction.

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

Literature:

1. Deshpande N et al. Rapid and ultra-rapid metabolizers with CYP2C19*17 polymorphism do not respond to standard therapy with proton pump inhibitors. Meta Gene 2016;9:159-64.
2. Dury S et al. Agranulocytosis induced by proton pump inhibitors. J Clin Gastroenterol 2012;46:859.
3. Hunfeld NG et al. A comparison of the acid-inhibitory effects of esomeprazole and pantoprazole in relation to pharmacokinetics and CYP2C19 polymorphism. Aliment Pharmacol Ther 2010;31:150-9.

Date 05-03-2018

CYP2C9 IM: fenprocoumon **1875**

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:

1. Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464.
2. Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.
3. Verhoef TI et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med 2013;369:2304-12.
4. Baranova EV et al. Dosing algorithms for vitamin K antagonists across VKORC1 and CYP2C9 genotypes. J Thromb Haemost 2017;15:465-472.
5. Abduljalil K. et al. Quantifying the effect of covariates on concentrations and effects of steady-state phenprocoumon using a population pharmacokinetic/pharmacodynamic model. Clin Pharmacokinet 2013;52:359-71.
6. Brehm K et al. Mechanical heart valve recipients: anticoagulation in patients with genetic variations of phenprocoumon metabolism. Eur J Cardiothorac Surg 2013;44:309-14.
7. Geisen C et al. Prediction of phenprocoumon maintenance dose and phenprocoumon plasma concentration by genetic and non-genetic parameters. Eur J Clin Pharmacol 2011;67:371-81.
8. Luxembourg B et al. Impact of pharmacokinetic (CYP2C9) and pharmacodynamic (VKORC1, F7, GGCX, CALU, EPHX1) gene variants on the initiation and maintenance phases of phenprocoumon therapy. Thromb Haemost 2011;105:169-80.
9. Cadamuro J et al. Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. Eur J Clin Pharmacol 2010;66:253-60.
10. Werner D et al. Pharmacogenetic characteristics of patients with complicated phenprocoumon dosing. Eur J Clin Pharmacol 2009;65:783-8.
11. Qazim B et al. Dependency of phenprocoumon dosage on polymorphisms in the VKORC1 and CYP2C9 genes. J Thromb Thrombolysis 2009;28:211-4.
12. Schalekamp T et al. VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. Clin Pharmacol Ther 2007;81:185-93.
13. Bohrer T et al. Left ventricular non-compaction associated with a genetic variant of the CYP2C9 gene. Heart Lung Circ 2006;15:269-71.
14. zu Schwabedissen CM et al. Obesity is associated with a slower response to initial phenprocoumon therapy whereas CYP2C9 genotypes are not. Eur J Clin Pharmacol 2006;62:713-20.
15. Visser LE et al. Allelic variants of cytochrome P450 2C9 modify the interaction between nonsteroidal anti-inflammatory drugs and coumarin anticoagulants. Clin Pharmacol Ther 2005;77:479-85.
16. Schalekamp T et al. Effects of cytochrome P450 2C9 polymorphisms on phenprocoumon anticoagulation status. Clin Pharmacol Ther 2004;76:409-17.
17. Ufer M et al. Genetic polymorphisms of cytochrome P450 2C9 causing reduced phenprocoumon (S)-7-hydroxylation in vitro and in vivo. Xenobiotica 2004;34:847-59.
18. Visser LE et al. The risk of bleeding complications in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Thromb Haemost 2004;92:61-6.
19. Visser LE et al. The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics 2004;14:27-33.
20. Kirchheiner J et al. Effects of CYP2C9 polymorphisms on the pharmacokinetics of R- and S-phenprocoumon in healthy volunteers. Pharmacogenetics 2004;14:19-26.
21. Hummers-Pradier E et al. Determination of bleeding risk using genetic markers in patients taking phenprocoumon. Eur J Clin Pharmacol 2003;59:213-9.

Date 14-05-2018

CYP2C9 PM: fenprocoumon **1876**

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:

1. Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464.
2. Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.
3. Verhoef TI et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med 2013;369:2304-12.
4. Baranova EV et al. Dosing algorithms for vitamin K antagonists across VKORC1 and CYP2C9 genotypes. J Thromb Haemost 2017;15:465-472.
5. Abduljalil K. et al. Quantifying the effect of covariates on concentrations and effects of steady-state phenprocoumon using a population pharmacokinetic/pharmacodynamic model. Clin Pharmacokinet 2013;52:359-71.
6. Brehm K et al. Mechanical heart valve recipients: anticoagulation in patients with genetic variations of phenprocoumon metabolism. Eur J Cardiothorac Surg 2013;44:309-14.
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9. Cadamuro J et al. Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. Eur J Clin Pharmacol 2010;66:253-60.
10. Werner D et al. Pharmacogenetic characteristics of patients with complicated phenprocoumon dosing. Eur J Clin Pharmacol 2009;65:783-8.
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20. Hummers-Pradier E et al. Determination of bleeding risk using genetic markers in patients taking phenprocoumon. Eur J Clin Pharmacol 2003;59:213-9.

Date 14-05-2018

CYP2C9*1/*2: fenprocoumon **1870**

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:

1. Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464.
2. Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.
3. Verhoef TI et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med 2013;369:2304-12.
4. Baranova EV et al. Dosing algorithms for vitamin K antagonists across VKORC1 and CYP2C9 genotypes. J Thromb Haemost 2017;15:465-472.
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6. Brehm K et al. Mechanical heart valve recipients: anticoagulation in patients with genetic variations of phenprocoumon metabolism. Eur J Cardiothorac Surg 2013;44:309-14.
7. Geisen C et al. Prediction of phenprocoumon maintenance dose and phenprocoumon plasma concentration by genetic and non-genetic parameters. Eur J Clin Pharmacol 2011;67:371-81.
8. Luxembourg B et al. Impact of pharmacokinetic (CYP2C9) and pharmacodynamic (VKORC1, F7, GGCX, CALU, EPHX1) gene variants on the initiation and maintenance phases of phenprocoumon therapy. Thromb Haemost 2011;105:169-80.
9. Cadamuro J et al. Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. Eur J Clin Pharmacol 2010;66:253-60.
10. Werner D et al. Pharmacogenetic characteristics of patients with complicated phenprocoumon dosing. Eur J Clin Pharmacol 2009;65:783-8.
11. Qazim B et al. Dependency of phenprocoumon dosage on polymorphisms in the VKORC1 and CYP2C9 genes. J Thromb Thrombolysis 2009;28:211-4.
12. Schalekamp T et al. VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. Clin Pharmacol Ther 2007;81:185-93.
13. Bohrer T et al. Left ventricular non-compaction associated with a genetic variant of the CYP2C9 gene. Heart Lung Circ 2006;15:269-71.
14. zu Schwabedissen CM et al. Obesity is associated with a slower response to initial phenprocoumon therapy whereas CYP2C9 genotypes are not. Eur J Clin Pharmacol 2006;62:713-20.
15. Visser LE et al. Allelic variants of cytochrome P450 2C9 modify the interaction between nonsteroidal anti-inflammatory drugs and coumarin anticoagulants. Clin Pharmacol Ther 2005;77:479-85.
16. Schalekamp T et al. Effects of cytochrome P450 2C9 polymorphisms on phenprocoumon anticoagulation status. Clin Pharmacol Ther 2004;76:409-17.
17. Ufer M et al. Genetic polymorphisms of cytochrome P450 2C9 causing reduced phenprocoumon (S)-7-hydroxylation in vitro and in vivo. Xenobiotica 2004;34:847-59.
18. Visser LE et al. The risk of bleeding complications in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Thromb Haemost 2004;92:61-6.
19. Visser LE et al. The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics 2004;14:27-33.
20. Kirchheiner J et al. Effects of CYP2C9 polymorphisms on the pharmacokinetics of R- and S-phenprocoumon in healthy volunteers. Pharmacogenetics 2004;14:19-26.
21. Hummers-Pradier E et al. Determination of bleeding risk using genetic markers in patients taking phenprocoumon. Eur J Clin Pharmacol 2003;59:213-9.

Date 14-05-2018

CYP2C9*1/*3: fenprocoumon **1871**

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:

1. Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464.
2. Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.
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13. zu Schwabedissen CM et al. Obesity is associated with a slower response to initial phenprocoumon therapy whereas CYP2C9 genotypes are not. Eur J Clin Pharmacol 2006;62:713-20.
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20. Hummers-Pradier E et al. Determination of bleeding risk using genetic markers in patients taking phenprocoumon. Eur J Clin Pharmacol 2003;59:213-9.

Date 14-05-2018

CYP2C9*2/*2: fenprocoumon **1872**

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:

1. Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464.
2. Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.
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6. Brehm K et al. Mechanical heart valve recipients: anticoagulation in patients with genetic variations of phenprocoumon metabolism. Eur J Cardiothorac Surg 2013;44:309-14.
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8. Werner D et al. Pharmacogenetic characteristics of patients with complicated phenprocoumon dosing. Eur J Clin Pharmacol 2009;65:783-8.
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10. Schalekamp T et al. VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. Clin Pharmacol Ther 2007;81:185-93.
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13. Schalekamp T et al. Effects of cytochrome P450 2C9 polymorphisms on phenprocoumon anticoagulation status. Clin Pharmacol Ther 2004;76:409-17.
14. Ufer M et al. Genetic polymorphisms of cytochrome P450 2C9 causing reduced phenprocoumon (S)-7-hydroxylation in vitro and in vivo. Xenobiotica 2004;34:847-59.

15. Visser LE et al. The risk of bleeding complications in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Thromb Haemost 2004;92:61-6.
16. Visser LE et al. The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics 2004;14:27-33.
17. Kirchheiner J et al. Effects of CYP2C9 polymorphisms on the pharmacokinetics of R- and S-phenprocoumon in healthy volunteers. Pharmacogenetics 2004;14:19-26.

Date 14-05-2018

CYP2C9*2/*3: fenprocoumon **1873**

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:

1. Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464.
2. Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.
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9. Cadamuro J et al. Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. Eur J Clin Pharmacol 2010;66:253-60.
10. Werner D et al. Pharmacogenetic characteristics of patients with complicated phenprocoumon dosing. Eur J Clin Pharmacol 2009;65:783-8.
11. Schalekamp T et al. VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. Clin Pharmacol Ther 2007;81:185-93.
12. zu Schwabedissen CM et al. Obesity is associated with a slower response to initial phenprocoumon therapy whereas CYP2C9 genotypes are not. Eur J Clin Pharmacol 2006;62:713-20.
13. Visser LE et al. Allelic variants of cytochrome P450 2C9 modify the interaction between nonsteroidal anti-inflammatory drugs and coumarin anticoagulants. Clin Pharmacol Ther 2005;77:479-85.
14. Schalekamp T et al. Effects of cytochrome P450 2C9 polymorphisms on phenprocoumon anticoagulation status. Clin Pharmacol Ther 2004;76:409-17.
15. Ufer M et al. Genetic polymorphisms of cytochrome P450 2C9 causing reduced phenprocoumon (S)-7-hydroxylation in vitro and in vivo. Xenobiotica 2004;34:847-59.
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17. Visser LE et al. The risk of overanticoagulation in patients with cytochrome P450 CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics 2004;14:27-33.
18. Kirchheiner J et al. Effects of CYP2C9 polymorphisms on the pharmacokinetics of R- and S-phenprocoumon in healthy volunteers. Pharmacogenetics 2004;14:19-26.
19. Hummers-Pradier E et al. Determination of bleeding risk using genetic markers in patients taking phenprocoumon. Eur J Clin Pharmacol 2003;59:213-9.

Date 14-05-2018

CYP2C9*3/*3: fenprocoumon **1874**

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:

1. Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.
2. Luxembourg B et al. Impact of pharmacokinetic (CYP2C9) and pharmacodynamic (VKORC1, F7, GGCX, CALU, EPHX1) gene variants on the initiation and maintenance phases of phenprocoumon therapy. Thromb Haemost 2011;105:169-80.
3. Werner D et al. Pharmacogenetic characteristics of patients with complicated phenprocoumon dosing. Eur J Clin Pharmacol 2009;65:783-8.
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5. Schalekamp T et al. Effects of cytochrome P450 2C9 polymorphisms on phenprocoumon anticoagulation status. Clin Pharmacol Ther 2004;76:409-17.
6. Ufer M et al. Genetic polymorphisms of cytochrome P450 2C9 causing reduced phenprocoumon (S)-7-hydroxylation in vitro and in vivo. Xenobiotica 2004;34:847-59.
7. Kirchheiner J et al. Effects of CYP2C9 polymorphisms on the pharmacokinetics of R- and S-phenprocoumon in healthy volunteers. Pharmacogenetics 2004;14:19-26.
8. Hummers-Pradier E et al. Determination of bleeding risk using genetic markers in patients taking phenprocoumon. Eur J Clin Pharmacol 2003;59:213-9.

Date 14-05-2018

VKORC1 -1639 AA: fenprocoumon **1912**

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 a anticoagulation clinic:
  - recommend to use 50% of the standard initial dose
  - recommend more frequent monitoring of the INR

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

Literature:

1. Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464.
2. Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.
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14. Cadamuro J et al. Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. Eur J Clin Pharmacol 2010;66:253-60.
15. Arnold ML et al. Pharmacogenetic testing for guiding de novo phenprocoumon therapy in stroke patients. Cerebrovasc Dis 2009;28:468-71.
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Date 10-09-2018

VKORC1 -1639 GA: fenprocoumon **1911**

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:

1. Zhang Y et al. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. J Thromb Haemost 2017;15:454-464.
2. Brehm K et al. Genetic variations of phenprocoumon metabolism in patients with ventricular assist devices. Eur J Cardiothorac Surg 2016;50:275-80.
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19. Reitsma PH et al. A C1173T dimorphism in the VKORC1 gene determines coumarin sensitivity and bleeding risk. PLoS Med 2005;2:e312.

Date 10-09-2018

CYP2C9 IM: fenytoine **1676**

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:

1. 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. Pharmacogenet Genomics 2016;26:225-34.
2. Ortega-Vázquez A et al. CYP2C9, CYP2C19, ABCB1 genetic polymorphisms and phenytoin plasma concentrations in Mexican-Mestizo patients with epilepsy. Pharmacogenomics J 2016;16:286-92.
3. Yamamoto Y et al. Individualized phenytoin therapy for Japanese pediatric patients with epilepsy based on CYP2C9 and CYP2C19 genotypes. Ther Drug Monit 2015;37:229-35.
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5. Depondt C et al. A candidate gene study of antiepileptic drug tolerability and -efficacy identifies an association of CYP2C9 variants with phenytoin toxicity. Eur J Neurol 2011;18:1159-64.
6. Kesavan R et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on phenytoin-induced neurological toxicity in Indian epileptic patients. Eur J Clin Pharmacol 2010;66:689-96.
7. Azzato EM et al. Maternal EPHX1 polymorphisms and risk of phenytoin-induced congenital malformations. Pharmacogenet Genomics 2010;20:58-63.
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9. McCluggage LK et al. Phenytoin toxicity due to genetic polymorphism. Neurocrit Care 2009;10:222-4.
10. Lee SY et al. Contributions of CYP2C9/CYP2C19 genotypes and drug interaction to the phenytoin treatment in the Korean epileptic patients in the clinical setting. J Biochem Mol Biol 2007;40:448-52.
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12. Hung CC et al. Dosage recommendation of phenytoin for patients with epilepsy with different CYP2C9/CYP2C19 polymorphisms. Ther Drug Monit 2004;26:534-40.
13. Van der Weide J et al. The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement. Pharmacogenetics 2001;11:287-91.
14. Ninomiya H et al. Genetic polymorphism of the CYP2C subfamily and excessive serum phenytoin concentration with central nervous system intoxication. Ther Drug Monit 2000;22:230-2.
15. Mamiya K et al. The effects of genetic polymorphisms of CYP2C9 and CYP2C19 on phenytoin metabolism in Japanese adult patients with epilepsy: studies in stereoselective hydroxylation and population pharmacokinetics. Epilepsia 1998;39:1317-23.
16. www.nvza.nl, TDM monografie voor fenytoïne.

Date 31-10-2016

CYP2C9 PM: fenytoine **1677**

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

Recommendation:

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

Literature:

1. Ortega-Vázquez A et al. CYP2C9, CYP2C19, ABCB1 genetic polymorphisms and phenytoin plasma concentrations in Mexican-Mestizo patients with epilepsy. Pharmacogenomics J 2016;16:286-92.
2. Kidd RS et al. Identification of a null allele of CYP2C9 in an African-American exhibiting toxicity to phenytoin. Pharmacogenetics 2001;11:803-8.

Date 31-10-2016

CYP2C9*1/*2: fenytoine **1678**

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:

1. Ortega-Vázquez A et al. CYP2C9, CYP2C19, ABCB1 genetic polymorphisms and phenytoin plasma concentrations in Mexican-Mestizo patients with epilepsy. Pharmacogenomics J 2016;16:286-92.
2. Depondt C et al. A candidate gene study of antiepileptic drug tolerability and -efficacy identifies an association of CYP2C9 variants with phenytoin toxicity. Eur J Neurol 2011;18:1159-64.
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7. Tate SK et al. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. Proc Natl Acad Sci U S A 2005;102:5507-12.
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11. Aynacioglu AS et al. Frequency of cytochrome P450 CYP2C9 variants in a Turkish population and functional relevance for phenytoin. Br J Clin Pharmacol 1999;48:409-15.
12. www.nvza.nl, TDM monografie voor fenytoïne.

Date 31-10-2016

CYP2C9*1/*3: fenytoine **1679**

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

Recommendation:

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

Literature:

1. 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. Pharmacogenet Genomics 2016;26:225-34.
2. Yamamoto Y et al. Individualized phenytoin therapy for Japanese pediatric patients with epilepsy based on CYP2C9 and CYP2C19 genotypes. Ther Drug Monit 2015;37:229-35.
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4. Hung CC et al. Effects of polymorphisms in six candidate genes on phenytoin maintenance therapy in Han Chinese patients. Pharmacogenomics 2012;13:1339-49.
5. Depondt C et al. A candidate gene study of antiepileptic drug tolerability and -efficacy identifies an association of CYP2C9 variants with phenytoin toxicity. Eur J Neurol 2011;18:1159-64.
6. Kesavan R et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on phenytoin-induced neurological toxicity in Indian epileptic patients. Eur J Clin Pharmacol 2010;66:689-96.
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8. Hennessy S et al. CYP2C9, CYP2C19, and ABCB1 genotype and hospitalization for phenytoin toxicity. J Clin Pharmacol 2009;49:1483-7.
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11. Rosemary J et al. Influence of the CYP2C9 AND CYP2C19 polymorphisms on phenytoin hydroxylation in healthy individuals from south India. Indian J Med Res 2006;123:665-70.
12. Hung CC et al. Dosage recommendation of phenytoin for patients with epilepsy with different CYP2C9/CYP2C19 polymorphisms. Ther Drug Monit 2004;26:534-40.
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16. Ninomiya H et al. Genetic polymorphism of the CYP2C subfamily and excessive serum phenytoin concentration with central nervous system intoxication. Ther Drug Monit 2000;22:230-2.
17. Aynacioglu AS et al. Frequency of cytochrome P450 CYP2C9 variants in a Turkish population and functional relevance for phenytoin. Br J Clin Pharmacol 1999;48:409-15.
18. Mamiya K et al. The effects of genetic polymorphisms of CYP2C9 and CYP2C19 on phenytoin metabolism in Japanese adult patients with epilepsy: studies in stereoselective hydroxylation and population pharmacokinetics. Epilepsia 1998;39:1317-23.
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21. www.nvza.nl, TDM monografie voor fenytoïne.

Date 31-10-2016

CYP2C9*2/*2: fenytoine **1680**

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

Recommendation:

1. The loading dose does not need to be adjusted.
2. For the other doses, use 50% 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:

1. Depondt C et al. A candidate gene study of antiepileptic drug tolerability and -efficacy identifies an association of CYP2C9 variants with phenytoin toxicity. Eur J Neurol 2011;18:1159-64.
2. Azzato EM et al. Maternal EPHX1 polymorphisms and risk of phenytoin-induced congenital malformations. Pharmacogenet Genomics 2010;20:58-63.
3. Hennessy S et al. CYP2C9, CYP2C19, and ABCB1 genotype and hospitalization for phenytoin toxicity. J Clin Pharmacol 2009;49:1483-7.
4. Tate SK et al. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. Proc Natl Acad Sci U S A 2005;102:5507-12.
5. Caraco Y et al. Phenytoin metabolic ratio: a putative marker of CYP2C9 activity in vivo. Pharmacogenetics 2001;11:587-96.
6. Van der Weide J et al. The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement. Pharmacogenetics 2001;11:287-91.
7. Kerb R et al. The predictive value of MDR1, CYP2C9, and CYP2C19 polymorphisms for phenytoin plasma levels. Pharmacogenomics J 2001;1:204-10.
8. Aynacioglu AS et al. Frequency of cytochrome P450 CYP2C9 variants in a Turkish population and functional relevance for phenytoin. Br J Clin Pharmacol 1999;48:409-15.
9. www.nvza.nl, TDM monografie voor fenytoïne.

Date 31-10-2016

CYP2C9*2/*3: fenytoine **1681**

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

Recommendation:

1. The loading dose does not need to be adjusted.
2. For the other doses, use 50% 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:

1. Kesavan R et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on phenytoin-induced neurological toxicity in Indian epileptic patients. Eur J Clin Pharmacol 2010;66:689-96.
2. Azzato EM et al. Maternal EPHX1 polymorphisms and risk of phenytoin-induced congenital malformations. Pharmacogenet Genomics 2010;20:58-63.
3. Caraco Y et al. Phenytoin metabolic ratio: a putative marker of CYP2C9 activity in vivo. Pharmacogenetics 2001;11:587-96.
4. Van der Weide J et al. The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement. Pharmacogenetics 2001;11:287-91.
5. www.nvza.nl, TDM monografie voor fenytoïne.

Date 31-10-2016

CYP2C9*3/*3: fenytoine **1682**

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

Recommendation:

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

Literature:

1. 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. Pharmacogenet Genomics 2016;26:225-34.
2. Chung WH et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. JAMA 2014;312:525-34.
3. Hung CC et al. Effects of polymorphisms in six candidate genes on phenytoin maintenance therapy in Han Chinese patients. Pharmacogenomics 2012;13:1339-49.
4. Kesavan R et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on phenytoin-induced neurological toxicity in Indian epileptic patients. Eur J Clin Pharmacol 2010;66:689-96.
5. Azzato EM et al. Maternal EPHX1 polymorphisms and risk of phenytoin-induced congenital malformations. Pharmacogenet Genomics 2010;20:58-63.
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8. Lee SY et al. Contributions of CYP2C9/CYP2C19 genotypes and drug interaction to the phenytoin treatment in the Korean epileptic patients in the clinical setting. J Biochem Mol Biol 2007;40:448-52.
9. Rosemary J et al. Influence of the CYP2C9 AND CYP2C19 polymorphisms on phenytoin hydroxylation in healthy individuals from south India. Indian J Med Res 2006;123:665-70.
10. Tate SK et al. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. Proc Natl Acad Sci U S A 2005;102:5507-12.
11. Brandolese R et al. Severe phenytoin intoxication in a subject homozygous for CYP2C9*3. Clin Pharmacol Ther 2001;70:391-4.
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13. Aynacioglu AS et al. Frequency of cytochrome P450 CYP2C9 variants in a Turkish population and functional relevance for phenytoin. Br J Clin Pharmacol 1999;48:409-15.
14. Kidd RS et al. Pharmacokinetics of chlorpheniramine, phenytoin, glipizide and nifedipine in an individual homozygous for the CYP2C9*3 allele. Pharmacogenetics 1999;9:71-80.
15. www.nvza.nl, TDM monografie voor fenytoïne.

Date 31-10-2016

CYP2D6 IM: flecainide **1593**

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:

1. Calvo D et al. Time-dependent responses to provocative testing with flecainide in the diagnosis of Brugada syndrome. Heart Rhythm 2015;12:350-7.
2. Hu M et al. Effects of CYP2D6*10, CYP3A5*3, CYP1A2*1F, and ABCB1 C3435T polymorphisms on the pharmacokinetics of flecainide in healthy Chinese subjects. Drug Metabol Drug Interact 2012;27:33-9.
3. Lim KS et al. Changes in the QTc interval after administration of flecainide acetate, with and without coadministered paroxetine, in relation to cytochrome P450 2D6 genotype: data from an open-label, two-period, single-sequence crossover study in healthy Korean male subjects. Clin Ther 2010;32:659-66.
4. Lim KS et al. Pharmacokinetic interaction of flecainide and paroxetine in relation to the CYP2D6*10 allele in healthy Korean subjects. Br J Clin Pharmacol 2008;66:660-6.
5. Doki K et al. Effect of CYP2D6 genotype on flecainide pharmacokinetics in Japanese patients with supraventricular tachyarrhythmia. Eur J Clin Pharmacol 2006;62:919-26.

Date 24-08-2016

CYP2D6 PM: flecainide **1592**

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:

1. Palmiere C et al. Usefulness of post-mortem biochemistry in forensic pathology: illustrative case reports. Leg Med (Tokyo) 2012;14:27-35.
2. Tenneze L et al. Pharmacokinetics and electrocardiographic effects of a new controlled-release form of flecainide acetate: comparison with the standard form and influence of the CYP2D6 polymorphism. Clin Pharmacol Ther 2002;72:112-22.
3. Funck-Brentano C et al. Variable disposition kinetics and electrocardiographic effects of flecainide during repeated dosing in humans: contribution of genetic factors, dose-dependent clearance, and interaction with amiodarone. Clin Pharmacol Ther 1994;55:256-69.
4. Gross AS et al. Polymorphic flecainide disposition under conditions of uncontrolled urine flow and pH. Eur J Clin Pharmacol 1991;40:155-62.
5. Gross AS et al. Stereoselective disposition of flecainide in relation to the sparteine/ debrisoquine metaboliser phenotype. Br J Clin Pharmacol 1989;28:555-66.
6. Mikus G et al. The influence of the sparteine/debrisoquin phenotype on the disposition of flecainide. Clin Pharmacol Ther 1989;45:562-7.

Date 24-08-2016

CYP2D6 UM: flecainide **1594**

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

Recommendation:

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

1. 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:
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Date 24-08-2016

HLA-B*5701: flucloxacilline **4652**

HLA-B*5701-positive patients have an 80-fold elevated risk of flucloxacillin-induced liver injury. However, the incidence is low (1-2 per 1000 individuals).

Recommendation:

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

Literature:

1. Vera JH et al. The safety of flucloxacillin in HIV-infected patients with positive HLA-B*5701 genotype. Aids 2013;27:484-5.
2. Philps EJ and Mallal SA. HLA-B*5701 and flucloxacillin associated drug-induced liver disease. Aids 2013;27:491-2.
3. Daly AK et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nature Genetics 2009;41:816-9.
4. SmPC Floxapen.

Date 20-11-2017

DPD AS 0: flucytosine **7209**

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

- Avoid flucytosine

Literature:

1. Mylan Healthcare LLC. Important risk information: Adapted recommendations for the use of flucytosine (Ancotil, solution for infusion 10 mg/ml, RVG 08533) in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. Direct Healthcare Professional Communication (Orange Hand Letter) 05-06-20.
2. SmPC Ancotil.

Date 14-09-2020

DPD AS 1,5: flucytosine **7210**

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 leukopaenia, neutropaenia, thrombocytopaenia 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:

1. Mylan Healthcare LLC. Important risk information: Adapted recommendations for the use of flucytosine (Ancotil, solution for infusion 10 mg/ml, RVG 08533) in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. Direct Healthcare Professional Communication (Orange Hand Letter) 05-06-20.
2. SmPC Ancotil.

Date 14-09-2020

DPD AS 1: flucytosine **7211**

A very low risk of severe toxicity is increased by gene variation. A small proportion of flucytosine is converted to fluorouracil. Patients with this gene variation are more likely to react to fluorouracil, but generally tolerate low doses (approximately 50% of the standard fluorouracil dose).

- Be alert to the occurrence of severe side effects, such as leukopaenia, neutropaenia, thrombocytopaenia 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:

1. Mylan Healthcare LLC. Important risk information: Adapted recommendations for the use of flucytosine (Ancotil, solution for infusion 10 mg/ml, RVG 08533) in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. Direct Healthcare Professional Communication (Orange Hand Letter) 05-06-20.
2. SmPC Ancotil.

Date 14-09-2020

DPD FENO: flucytosine **7208**

A very low risk of severe toxicity is increased by gene variation. A small proportion of flucytosine is converted to fluorouracil. Patients with this gene variation are more likely to have a reaction to fluorouracil, but generally tolerate low doses (15-50% of the standard fluorouracil dose).

- Be alert to the occurrence of severe side effects, such as leukopaenia, neutropaenia, thrombocytopaenia 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:

1. Mylan Healthcare LLC. Important risk information: Adapted recommendations for the use of flucytosine (Ancotil, solution for infusion 10 mg/ml, RVG 08533) in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. Direct Healthcare Professional Communication (Orange Hand Letter) 05-06-20.
2. SmPC Ancotil.

Date 14-09-2020

DPD AS 0: fluorouracil cutaan **6192**

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:

1. Henricks LM et al. Capecitabine-based treatment of a patient with a novel DPYD genotype and complete dihydropyrimidine dehydrogenase deficiency. Int J Cancer 2018;142:424-30.
2. Henricks LM et al. Treatment algorithm for homozygous or compound heterozygous DPYD variant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.
3. Kodali S et al. Capecitabine-induced severe toxicity secondary to DPD deficiency and successful treatment with low dose 5-fluorouracil. J Gastrointest Cancer 2017;48:66-69.
4. Lunenburg CA et al. Evaluation of clinical implementation of prospective DPYD genotyping in 5-fluorouracil- or capecitabine-treated patients. Pharmacogenomics 2016;17:721-9.
5. Deenen MJ et al. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. J Clin Oncol 2016;34:227-34.
6. Rosmarin D et al. Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: investigation in the QUASAR2 study, systematic review, and meta-analysis. J Clin Oncol 2014; 32:1031-9.
7. Deenen MJ et al. Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. Clin Cancer Res 2011; 17:3455-68.
8. Gross E et al. Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients. PLoS ONE 2008;3:e4003.
9. Boisdron-Celle M et al. 5-Fluorouracil-related severe toxicity: a comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency. Cancer Lett 2007;249:271-82.
10. Morel A et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther 2006;5:2895-904.
11. Van Kuilenburg AB et al. High prevalence of the IVS14 + 1G>A mutation in the dihydropyrimidine dehydrogenase gene of patients with severe 5-fluorouracil-associated toxicity. Pharmacogenetics 2002;12:555-8.
12. Raida M et al. Prevalence of a common point mutation in the dihydropyrimidine dehydrogenase (DPD) gene within the 5'-splice donor site of intron 14 in patients with severe 5-fluorouracil (5-FU)-related toxicity compared with controls. Clin Cancer Res 2001;7:2832-9.
13. van Kuilenburg AB et al. Clinical implications of dihydropyrimidine dehydrogenase (DPD) deficiency in patients with severe 5-fluorouracil-associated toxicity: identification of new mutations in the DPD gene. Clin Cancer Res 2000;6:4705-12.
14. Johnson MR et al. Life-threatening toxicity in a dihydropyrimidine dehydrogenase-deficient patient after treatment with topical 5-fluorouracil. Clin Cancer Res 1999;5:2006-11.
15. SPC Efudix crème en Carac cream (VS).

Date 13-05-2019

DPD AS 1,5: fluorouracil/capecitabine **4894**

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:

1. Kleinjan JP et al. Tolerance-based capecitabine dose escalation after DPYD genotype-guided dosing in heterozygote DPYD variant carriers: a single-center observational study. Anticancer Drugs 2019 Jan 8 [Epub ahead of print].
2. Lunenburg CATC et al. Diagnostic and therapeutic strategies for fluoropyrimidine treatment of patients carrying multiple DPYD variants. Genes (Basel) 2018;9:E585.
3. Lunenburg CATC et al. Standard fluoropyrimidine dosages in chemoradiation therapy result in an increased risk of severe toxicity in DPYD variant allele carriers. Eur J Cancer 2018;104:210-8.
4. Henricks LM et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. Lancet Oncol 2018;19:1459-67 en persoonlijke communicatie (getitreerde dosis en mediane DPD-activiteit).
5. Madi A et al. Pharmacogenetic analyses of 2183 patients with advanced colorectal cancer; potential role for common dihydropyrimidine dehydrogenase variants in toxicity to chemotherapy. Eur J Cancer 2018;102:31-9.
6. Meulendijks D et al. Pretreatment serum uracil concentration as a predictor of severe and fatal fluoropyrimidine-associated toxicity. Br J Cancer 2017;116:1415-24.
7. Lunenburg CA et al. Evaluation of clinical implementation of prospective DPYD genotyping in 5-fluorouracil- or capecitabine-treated patients. Pharmacogenomics 2016;17:721-9.
8. Lee AM et al. Association between DPYD c.1129-5923 C>G/hapB3 and severe toxicity to 5-fluorouracil-based chemotherapy in stage III colon cancer patients: NCCTG N0147 (Alliance). Pharmacogenet Genomics 2016;26:133-7.
9. Meulendijks D et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16:1639-50.
10. Lee AM et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). J Natl Cancer Inst 2014;106:dju298.
11. Rosmarin D et al. Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: investigation in the QUASAR2 study, systematic review, and meta-analysis. J Clin Oncol 2014; 32:1031-9.
12. Terrazzino S et al. DPYD IVS14+1 G>A and 2846A>T genotyping for the prediction of severe fluoropyrimidine-related toxicity: a meta-analysis. Pharmacogenomics2013; 14:1255-72.
13. Deenen MJ et al. Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. Clin Cancer Res 2011; 17:3455-68.
14. Kristensen MH et al. Variants in the dihydropyrimidine dehydrogenase, methylenetetrahydrofolate reductase and thymidylate synthase genes predict early toxicity of 5-fluorouracil in colorectal cancer patients. J Int Med Res 2010; 38:870-83.
15. Gross E et al. Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients. PLoS ONE 2008;3:e4003.
16. Capitain O et al. The influence of fluorouracil outcome parameters on tolerance and efficacy in patients with advanced colorectal cancer. Pharmacogenomics J 2008;8:256-67.

17. Boisdron-Celle M et al. 5-Fluorouracil-related severe toxicity: a comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency. Cancer Lett 2007;249:271-82.
18. Cho HJ et al. Thymidylate synthase (TYMS) and dihydropyrimidine dehydrogenase (DPYD) polymorphisms in the Korean population for prediction of 5-fluorouracil-associated toxicity. Ther Drug Monit 2007;29:190-6.
19. Morel A et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther 2006;5:2895-904.
20. Yamaguchi K et al. Germline mutation of dihydropyrimidine dehydrogenese gene among a Japanese population in relation to toxicity to 5-fluorouracil. Jpn J Cancer Res 2001;92:337-42.
21. van Kuilenburg AB et al. Clinical implications of dihydropyrimidine dehydrogenase (DPD) deficiency in patients with severe 5-fluorouracil-associated toxicity: identification of new mutations in the DPD gene. Clin Cancer Res 2000;6:4705-12.
22. SPC's Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS) en Xeloda (VS).

Date 13-05-2019

DPD AS 1: fluorouracil/capecitabine **2552**

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

- Start with 50% of the standard dose or avoid fluorouracil and capecitabine.
  Adjustment of the subsequent dose should be guided by toxicity and effectiveness. However, in one study involving 17 patients with gene 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:

1. Kleinjan JP et al. Tolerance-based capecitabine dose escalation after DPYD genotype-guided dosing in heterozygote DPYD variant carriers: a single-center observational study. Anticancer Drugs 2019 Jan 8 [Epub ahead of print].
2. Henricks LM et al. Effectiveness and safety of reduced-dose fluoropyrimidine therapy in patients carrying the DPYD*2A variant: a matched pair analysis. Int J Cancer 2018 Nov 28 [Epub ahead of print].
3. Lunenburg CATC et al. Standard fluoropyrimidine dosages in chemoradiation therapy result in an increased risk of severe toxicity in DPYD variant allele carriers. Eur J Cancer 2018;104:210-8.
4. Henricks LM et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. Lancet Oncol 2018;19:1459-67 en persoonlijke communicatie (getitreerde dosis en mediane DPD-activiteit).
5. Madi A et al. Pharmacogenetic analyses of 2183 patients with advanced colorectal cancer; potential role for common dihydropyrimidine dehydrogenase variants in toxicity to chemotherapy. Eur J Cancer 2018;102:31-9.
6. Meulendijks D et al. Pretreatment serum uracil concentration as a predictor of severe and fatal fluoropyrimidine-associated toxicity. Br J Cancer 2017;116:1415-24.
7. Kodali S et al. Capecitabine-induced severe toxicity secondary to DPD deficiency and successful treatment with low dose 5-fluorouracil. J Gastrointest Cancer 2017;48:66-69.
8. Meulendijks D et al. Patients homozygous for DPYD c.1129-5923C>G/ haplotype B3 have partial DPD deficiency and require a dose reduction when treated with fluoropyrimidines. Cancer Chemother Pharmacol 2016;78:875-80.
9. Lunenburg CA et al. Evaluation of clinical implementation of prospective DPYD genotyping in 5-fluorouracil- or capecitabine-treated patients. Pharmacogenomics 2016;17:721-9.
10. Deenen MJ et al. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. J Clin Oncol 2016;34:227-34.
11. Meulendijks D et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16:1639-50.
12. Lee AM et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). J Natl Cancer Inst 2014;106:dju298.
13. Rosmarin D et al. Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: investigation in the QUASAR2 study, systematic review, and meta-analysis. J Clin Oncol 2014; 32:1031-9.
14. Terrazzino S et al. DPYD IVS14+1 G>A and 2846A>T genotyping for the prediction of severe fluoropyrimidine-related toxicity: a meta-analysis. Pharmacogenomics 2013;14:1255-72.
15. Magnani E et al. Fluoropyrimidine toxicity in patients with dihydropyrimidine dehydrogenase splice site variant: the need for further revision of dose and schedule. Intern Emerg Med 2013; 8:417-23.
16. Vulsteke C et al. Genetic variability in the multidrug resistance associated protein-1 (ABCC1/MRP1) predicts hematological toxicity in breast cancer patients receiving (neo-)adjuvant chemotherapy with 5-fluorouracil, epirubicin and cyclophosphamide (FEC). Ann Oncol 2013; 24:1513-25.
17. van Kuilenburg AB et al. Evaluation of 5-fluorouracil pharmacokinetics in cancer patients with a c.1905+1 G>A mutation in DPYD by means of a Bayesian limited sampling strategy. Clin Pharmacokinet 2012;51:163-74.
18. Deenen MJ et al. Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. Clin Cancer Res 2011; 17:3455-68.
19. Gross E et al. Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients. PLoS ONE 2008;3:e4003.
20. Capitain O et al. The influence of fluorouracil outcome parameters on tolerance and efficacy in patients with advanced colorectal cancer. Pharmacogenomics J 2008;8:256-67.
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26. Saif MW et al. Dihydropyrimidine dehydrogenase deficiency (GPD) in GI malignancies: experience of 4-years. Pak J Med Sci Q 2007;23:832-9.
27. Boisdron-Celle M et al. 5-Fluorouracil-related severe toxicity: a comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency. Cancer Lett 2007;249:271-82.
28. Cho HJ et al. Thymidylate synthase (TYMS) and dihydropyrimidine dehydrogenase (DPYD) polymorphisms in the Korean population for prediction of 5-fluorouracil-associated toxicity. Ther Drug Monit 2007;29:190-6.
29. Salgado J et al. Polymorphisms in the thymidylate synthase and dihydropyrimidine dehydrogenase genes predict response and toxicity to capecitabine-raltitrexed in colorectal cancer. Oncol Rep 2007;17:325-8.
30. Morel A et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther 2006;5:2895-904.
31. Largillier R et al. Pharmacogenetics of capecitabine in advanced breast cancer patients. Clin Cancer Res 2006;12:5496-502.
32. Salgueiro N et al. Mutations in exon 14 of dihydropyrimidine dehydrogenase and 5-Fluorouracil toxicity in Portuguese colorectal cancer patients. Genet Med 2004;6:102-7.
33. Van Kuilenburg AB et al. High prevalence of the IVS14 + 1G>A mutation in the dihydropyrimidine dehydrogenase gene of patients with severe 5-fluorouracil-associated toxicity. Pharmacogenetics 2002;12:555-8.
34. Raida M et al. Prevalence of a common point mutation in the dihydropyrimidine dehydrogenase (DPD) gene within the 5'-splice donor site of intron 14 in patients with severe 5-fluorouracil (5-FU)- related toxicity compared with controls. Clin Cancer Res 2001;7:2832-9.
35. van Kuilenburg AB et al. Clinical implications of dihydropyrimidine dehydrogenase (DPD) deficiency in patients with severe 5-fluorouracil-associated toxicity: identification of new mutations in the DPD gene. Clin Cancer Res 2000;6:4705-12.
36. SPC's Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS) en Xeloda (VS).

Date 13-05-2019

DPD FENO: fluorouracil/capecitabine **4893**

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:

1. Lunenburg CATC et al. Diagnostic and therapeutic strategies for fluoropyrimidine treatment of patients carrying multiple DPYD variants. Genes (Basel) 2018;9:E585.
2. Lunenburg CATC et al. Standard fluoropyrimidine dosages in chemoradiation therapy result in an increased risk of severe toxicity in DPYD variant allele carriers. Eur J Cancer 2018;104:210-8.
3. Henricks LM et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. Lancet Oncol 2018;19:1459-67 en persoonlijke communicatie (getitreerde dosis en mediane DPD-activiteit).
4. Henricks LM et al. Treatment algorithm for homozygous or compound heterozygous DPYD variant allele carriers with low-dose capecitabine. JCO Precis Oncol 2017 - published online Oct 6.
5. Kodali S et al. Capecitabine-induced severe toxicity secondary to DPD deficiency and successful treatment with low dose 5-fluorouracil. J Gastrointest Cancer 2017;48:66-69.
6. Meulendijks D et al. Patients homozygous for DPYD c.1129-5923C>G/ haplotype B3 have partial DPD deficiency and require a dose reduction when treated with fluoropyrimidines. Cancer Chemother Pharmacol 2016;78:875-80.
7. Lunenburg CA et al. Evaluation of clinical implementation of prospective DPYD genotyping in 5-fluorouracil- or capecitabine-treated patients. Pharmacogenomics 2016;17:721-9.
8. Lee AM et al. Association between DPYD c.1129-5923 C>G/hapB3 and severe toxicity to 5-fluorouracil-based chemotherapy in stage III colon cancer patients: NCCTG N0147 (Alliance). Pharmacogenet Genomics 2016;26:133-7.
9. Deenen MJ et al. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. J Clin Oncol 2016;34:227-34.
10. Meulendijks D et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16:1639-50.
11. Lee AM et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). J Natl Cancer Inst 2014;106:dju298.

12. Deenen MJ et al. Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. Clin Cancer Res 2011; 17:3455-68.
13. Boisdron-Celle M et al. 5-Fluorouracil-related severe toxicity: a comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency. Cancer Lett 2007;249:271-82.
14. Morel A et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther 2006;5:2895-904.
15. SPC's Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS) en Xeloda (VS).

Date 13-05-2019

DPD AS 0: fluorouracil/capecitabine,systemisch **2551**

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:

1. Henricks LM et al. Capecitabine-based treatment of a patient with a novel DPYD genotype and complete dihydropyrimidine dehydrogenase deficiency. Int J Cancer 2018;142:424-30.
2. Henricks LM et al. Treatment algorithm for homozygous or compound heterozygous DPYD variant allele carriers with low-dose capecitabine. JCO Precis Oncol - published online 2017 Oct 6.
3. Kodali S et al. Capecitabine-induced severe toxicity secondary to DPD deficiency and successful treatment with low dose 5-fluorouracil. J Gastrointest Cancer 2017;48:66-69.
4. Meulendijks D et al. Patients homozygous for DPYD c.1129-5923C>G/ haplotype B3 have partial DPD deficiency and require a dose reduction when treated with fluoropyrimidines. Cancer Chemother Pharmacol 2016;78:875-80.
5. Lunenburg CA et al. Evaluation of clinical implementation of prospective DPYD genotyping in 5-fluorouracil- or capecitabine-treated patients. Pharmacogenomics 2016;17:721-9.
6. Deenen MJ et al. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. J Clin Oncol 2016;34:227-34.
7. Rosmarin D et al. Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: investigation in the QUASAR2 study, systematic review, and meta-analysis. J Clin Oncol 2014; 32:1031-9.
8. Deenen MJ et al. Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. Clin Cancer Res 2011; 17:3455-68.
9. Gross E et al. Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients. PLoS ONE 2008;3:e4003.
10. Boisdron-Celle M et al. 5-Fluorouracil-related severe toxicity: a comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency. Cancer Lett 2007;249:271-82.
11. Morel A et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther 2006;5:2895-904.
12. Van Kuilenburg AB et al. High prevalence of the IVS14 + 1G>A mutation in the dihydropyrimidine dehydrogenase gene of patients with severe 5-fluorouracil-associated toxicity. Pharmacogenetics 2002;12:555-8.
13. Raida M et al. Prevalence of a common point mutation in the dihydropyrimidine dehydrogenase (DPD) gene within the 5'-splice donor site of intron 14 in patients with severe 5-fluorouracil (5-FU)- related toxicity compared with controls. Clin Cancer Res 2001;7:2832-9.
14. van Kuilenburg AB et al. Clinical implications of dihydropyrimidine dehydrogenase (DPD) deficiency in patients with severe 5-fluorouracil-associated toxicity: identification of new mutations in the DPD gene. Clin Cancer Res 2000;6:4705-12.
15. Johnson MR et al. Life-threatening toxicity in a dihydropyrimidine dehydrogenase-deficient patient after treatment with topical 5-fluorouracil. Clin Cancer Res 1999;5:2006-11.
16. SPC's Fluorouracil PCH, Xeloda, Efudix crème, Fluorouracil (VS), Xeloda (VS) en Carac cream (VS).

Date 13-05-2019

CYP2D6 IM: fluoxetine **5997**

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:

1. Gassó P et al. Effect of CYP2D6, CYP2C9 and ABCB1 genotypes on fluoxetine plasma concentrations and clinical improvement in children and adolescent patients. Pharmacogenomics J 2014;14:457-62.
2. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.
3. Scordo MG et al. Influence of CYP2C9, 2C19 and 2D6 genetic polymorphisms on the steady-state plasma concentrations of the enantiomers of fluoxetine and norfluoxetine. Basic Clin Pharmacol Toxicol 2005;97:296-301.
4. LLerena A et al. Effect of CYP2D6 and CYP2C9 genotypes on fluoxetine and norfluoxetine plasma concentrations during steady-state conditions. Eur J Clin Pharmacol 2004;59:869-73.

Date 14-05-2018

CYP2D6 PM: fluoxetine **5996**

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:

1. Gassó P et al. Effect of CYP2D6, CYP2C9 and ABCB1 genotypes on fluoxetine plasma concentrations and clinical improvement in children and adolescent patients. Pharmacogenomics J 2014;14:457-62.
2. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.
3. Scordo MG et al. Influence of CYP2C9, 2C19 and 2D6 genetic polymorphisms on the steady-state plasma concentrations of the enantiomers of fluoxetine and norfluoxetine. Basic Clin Pharmacol Toxicol 2005;97:296-301.
4. LLerena A et al. Effect of CYP2D6 and CYP2C9 genotypes on fluoxetine and norfluoxetine plasma concentrations during steady-state conditions. Eur J Clin Pharmacol 2004;59:869-73.
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.
6. Perucca E et al. Fluoxetine-induced movement disorders and deficient CYP2D6 enzyme activity. Mov Disord 1997;12:624-5.
7. SPC Prozac, USA, 30-01-09.

Date 14-05-2018

CYP2D6 UM: fluoxetine **5998**

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:

1. Gassó P et al. Effect of CYP2D6, CYP2C9 and ABCB1 genotypes on fluoxetine plasma concentrations and clinical improvement in children and adolescent patients. Pharmacogenomics J 2014;14:457-62.
2. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.
3. Scordo MG et al. Influence of CYP2C9, 2C19 and 2D6 genetic polymorphisms on the steady-state plasma concentrations of the enantiomers of fluoxetine and norfluoxetine. Basic Clin Pharmacol Toxicol 2005;97:296-301.
4. LLerena A et al. Effect of CYP2D6 and CYP2C9 genotypes on fluoxetine and norfluoxetine plasma concentrations during steady-state conditions. Eur J Clin Pharmacol 2004;59:869-73.

Date 14-05-2018

CYP2D6 IM: flupentixol **1532**

This is NOT a gene-drug interaction.

No studies have been published in which the kinetics and the effects of flupentixol were studied for this phenotype.

Literature:
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Date 14-09-2020

CYP2D6 PM: flupentixol **1534**

This is NOT a gene-drug interaction.

No studies have been published in which the kinetics and the effects of flupentixol were studied for this phenotype.

Literature:

Date 14-09-2020

CYP2D6 UM: flupentixol **1533**

This is NOT a gene-drug interaction.

No studies have been published in which the kinetics and the effects of flupentixol were studied for this phenotype.

Literature:
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Date 14-09-2020

SLCO1B1 521CC: fluvastatine **4060**

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:

1. Hirvensalo P et al. Enantiospecific pharmacogenomics of fluvastatin. Clin Pharmacol Ther 2019;106:668-80.
2. Mori D et al. Effect of OATP1B1 genotypes on plasma concentrations of endogenous OATP1B1 substrates and drugs, and their association in healthy volunteers. Drug Metab Pharmacokinet 2019;34:78-86.
3. Xiang Q et al. The association between the SLCO1B1, apolipoprotein E, and CYP2C9 genes and lipid response to fluvastatin: a meta-analysis. Pharmacogenet Genomics 2018;28:261-7.
4. Meyer zu Schwabedissen HE et al. Function-impairing polymorphisms of the hepatic uptake transporter SLCO1B1 modify the therapeutic efficacy of statins in a population-based cohort. Pharmacogenet Genomics 2015;25:8-18.
5. Pasanen MK et al. Polymorphism of the hepatic influx transporter organic anion transporting polypeptide 1B1 is associated with increased cholesterol synthesis rate. Pharmacogenet Genomics 2008;18:921-6.
6. Couvert P et al. Association between a frequent allele of the gene encoding OATP1B1 and enhanced LDL-lowering response to fluvastatin therapy. Pharmacogenomics 2008;9:1217-27.
7. Singer JB et al. Genetic analysis of fluvastatin response and dyslipidemia in renal transplant recipients. J Lipid Res 2007;48:2072-8.
8. Niemi M et al. SLCO1B1 polymorphism and sex affect the pharmacokinetics of pravastatin but not fluvastatin. Clin Pharmacol Ther 2006;80:356-66.
9. Thompson JF et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharmacogenomics J 2005;5:352-8.

Date 18-05-2020

SLCO1B1 521TC: fluvastatine **4059**

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:

1. Hirvensalo P et al. Enantiospecific pharmacogenomics of fluvastatin. Clin Pharmacol Ther 2019;106:668-80.
2. Mori D et al. Effect of OATP1B1 genotypes on plasma concentrations of endogenous OATP1B1 substrates and drugs, and their association in healthy volunteers. Drug Metab Pharmacokinet 2019;34:78-86.
3. Xiang Q et al. The association between the SLCO1B1, apolipoprotein E, and CYP2C9 genes and lipid response to fluvastatin: a meta-analysis. Pharmacogenet Genomics 2018;28:261-7.
4. Meyer zu Schwabedissen HE et al. Function-impairing polymorphisms of the hepatic uptake transporter SLCO1B1 modify the therapeutic efficacy of statins in a population-based cohort. Pharmacogenet Genomics 2015;25:8-18.
5. Pasanen MK et al. Polymorphism of the hepatic influx transporter organic anion transporting polypeptide 1B1 is associated with increased cholesterol synthesis rate. Pharmacogenet Genomics 2008;18:921-6.

6. Couvert P et al. Association between a frequent allele of the gene encoding OATP1B1 and enhanced LDL-lowering response to fluvastatin therapy. Pharmacogenomics 2008;9:1217-27.
7. Singer JB et al. Genetic analysis of fluvastatin response and dyslipidemia in renal transplant recipients. J Lipid Res 2007;48:2072-8.
8. Niemi M et al. SLCO1B1 polymorphism and sex affect the pharmacokinetics of pravastatin but not fluvastatin. Clin Pharmacol Ther 2006;80:356-66.
9. Thompson JF et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharmacogenomics J 2005;5:352-8.

Date 18-05-2020

CYP2C19 IM: fluvoxamine **3510**

This is NOT a gene-drug interaction

Literature:

1. Jan MW et al. Pharmacokinetics of fluvoxamine in relation to CYP2C19 phenotype and genotype. Drug Metabol Drug Interact 2002;19:1-11.
2. Spigset O et al. The major fluvoxamine metabolite in urine is formed by CYP2D6. Eur J Clin Pharmacol 2001;57:653-8.
3. Spigset O et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. Eur J Clin Pharmacol 1997;52:129-33.

Date 14-05-2018

CYP2C19 PM: fluvoxamine **3509**

This is NOT a gene-drug interaction.

Literature:

1. Jan MW et al. Pharmacokinetics of fluvoxamine in relation to CYP2C19 phenotype and genotype. Drug Metabol Drug Interact 2002;19:1-11.
2. Spigset O et al. The major fluvoxamine metabolite in urine is formed by CYP2D6. Eur J Clin Pharmacol 2001;57:653-8.
3. Spigset O et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. Eur J Clin Pharmacol 1997;52:129-33.

Date 14-05-2018

CYP2C19 UM: fluvoxamine **3511**

This is NOT a gene-drug interaction.

Literature:

1. Jan MW et al. Pharmacokinetics of fluvoxamine in relation to CYP2C19 phenotype and genotype. Drug Metabol Drug Interact 2002;19:1-11.
2. Spigset O et al. The major fluvoxamine metabolite in urine is formed by CYP2D6. Eur J Clin Pharmacol 2001;57:653-8.
3. Spigset O et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. Eur J Clin Pharmacol 1997;52:129-33.

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.

Literature:

1. Suzuki Y et al. CYP2D6 genotype and smoking influence fluvoxamine steady-state concentration in Japanese psychiatric patients: lessons for genotype-phenotype association study design in translational pharmacogenetics. J Psychopharmacol 2011;25:908-14.
2. Sugahara H et al. Effect of smoking and CYP2D6 polymorphisms on the extent of fluvoxamine-alprazolam interaction in patients with psychosomatic disease. Eur J Clin Pharmacol 2009;65:699-704.
3. Suzuki Y et al. Polymorphisms in the 5-hydroxytryptamine 2A receptor and cytochromeP4502D6 genes synergistically predict fluvoxamine-induced side effects in Japanese depressed patients. Neuropsychopharmacology 2006;31:825-31.
4. Gerstenberg G et al. Effects of the CYP2D6 genotype and cigarette smoking on the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. Ther Drug Monit 2003;25:463-8.
5. Gerstenberg G et al. Relationship between clinical effects of fluvoxamine and the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. Psychopharmacology (Berl) 2003;167:443-8.
6. Ohara K et al. CYP2D6*10 alleles do not determine plasma fluvoxamine concentration/dose ratio in Japanese subjects. Eur J Clin Pharmacol 2003;58:659-61.

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.

Literature:

1. Christensen M et al. Low daily 10-mg and 20-mg doses of fluvoxamine inhibit the metabolism of both caffeine (cytochrome P4501A2) and omeprazole (cytochrome P4502C19). Clin Pharmacol Ther 2002;71:141-52.
2. Spigset O et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. Eur J Clin Pharmacol 1997;52:129-33.
3. Carrillo JA et al. Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. Clin Pharmacol Ther 1996;60:183-90.

4. SPC's Fevarin en Luvox (VS).

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 substantation of a reduced effectiveness.

Literature:

1. Suzuki Y et al. CYP2D6 genotype and smoking influence fluvoxamine steady-state concentration in Japanese psychiatric patients: lessons for genotype-phenotype association study design in translational pharmacogenetics. J Psychopharmacol 2011;25:908-14.
2. Spigset O et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. Eur J Clin Pharmacol 1997;52:129-33.
3. Carrillo JA et al. Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. Clin Pharmacol Ther 1996;60:183-90.

Date 14-05-2018

CYP2D6 IM: gefitinib **4871**

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:

1. Hirose T et al. Association of pharmacokinetics and pharmacogenomics with safety and efficacy of gefitinib in patients with EGFR mutation positive advanced non-small cell lung cancer. Lung Cancer 2016;93:69-76.
2. Sugiyama E et al. Impact of single nucleotide polymorphisms on severe hepatotoxicity induced by EGFR tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. Lung Cancer 2015;90:307-13.
3. Kobayashi H et al. Relationship among gefitinib exposure, polymorphisms of its metabolizing enzymes and transporters, and side effects in Japanese patients with non-small-cell lung cancer. Clin Lung Cancer 2015;16:274-81.
4. Takimoto T et al. Polymorphisms of CYP2D6 gene and gefitinib-induced hepatotoxicity. Clinical Lung Cancer 2013;14:502-7.
5. Suzumura T et al. Reduced CYP2D6 function is associated with gefitinib-induced rash in patients with non-small cell lung cancer. BMC Cancer 2012;12:568.
6. Chhun S et al. Gefitinib-phenytoin interaction is not correlated with the C-erythromycin breath test in healthy male volunteers. Br J Clin Pharmacol 2009;68:226-37.

Date 19-11-2018

CYP2D6 PM: gefitinib **4872**

NO action is needed for this gene-drug interaction.

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

Literature:

1. Chhun S et al. Gefitinib-phenytoin interaction is not correlated with the C-erythromycin breath test in healthy male volunteers. Br J Clin Pharmacol 2009;68:226-37.
2. Swaisland HC et al. Exploring the relationship between expression of cytochrome P450 enzymes and gefitinib pharmacokinetics. Clin Pharmacokinet 2006;45:633-44.
3. SPC Iressa.

Date 19-11-2018

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.

Literature:

1. Chhun S et al. Gefitinib-phenytoin interaction is not correlated with the C-erythromycin breath test in healthy male volunteers. Br J Clin Pharmacol 2009;68:226-37.
2. Swaisland HC et al. Exploring the relationship between expression of cytochrome P450 enzymes and gefitinib pharmacokinetics. Clin Pharmacokinet 2006;45:633-44.
3. SPC Iressa.

Date 19-11-2018

CYP2C9 IM: 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.

Literature:

1. Surendiran A et al. Influence of CYP2C9 gene polymorphisms on response to glibenclamide in type 2 diabetes mellitus patients. Eur J Clin Pharmacol 2011;67:797-801.
2. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
3. Yin OQ et al. CYP2C9, but not CYP2C19, polymorphisms affect the pharmacokinetics and pharmacodynamics of glyburide in Chinese subjects. Clin Pharmacol Ther 2005;78:370-7.
4. Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.
5. Kirchheiner J et al. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. Clin Pharmacol Ther 2002;71:286-96.

Date 20-11-2017

CYP2C9 PM: glibenclamide **1883**

NO action is required for this gene-drug interaction.

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

Literature:

1. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
2. Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.
3. Kirchheiner J et al. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. Clin Pharmacol Ther 2002;71:286-96.

Date 20-11-2017

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.

Literature:

1. Surendiran A et al. Influence of CYP2C9 gene polymorphisms on response to glibenclamide in type 2 diabetes mellitus patients. Eur J Clin Pharmacol 2011;67:797-801.
2. Becker ML et al. Cytochrome P450 2C9 *2 and* 3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
3. Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.
4. Kirchheiner J et al. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. Clin Pharmacol Ther 2002;71:286-96.

Date 20-11-2017

CYP2C9*1/*3: glibenclamide **1878**

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:

1. Surendiran A et al. Influence of CYP2C9 gene polymorphisms on response to glibenclamide in type 2 diabetes mellitus patients. Eur J Clin Pharmacol 2011;67:797-801.
2. Becker ML et al. Cytochrome P450 2C9 *2 and* 3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
3. Yin OQ et al. CYP2C9, but not CYP2C19, polymorphisms affect the pharmacokinetics and pharmacodynamics of glyburide in Chinese subjects. Clin Pharmacol Ther 2005;78:370-7.
4. Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.
5. Kirchheiner J et al. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. Clin Pharmacol Ther 2002;71:286-96.

Date 20-11-2017

CYP2C9*2/*2: glibenclamide **1879**

NO action is required for this gene-drug interaction.

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

Literature:

1. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
2. Kirchheiner J et al. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. Clin Pharmacol Ther 2002;71:286-96.

Date 20-11-2017

CYP2C9*2/*3: glibenclamide **1880**

NO action is required for this gene-drug interaction.

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

Literature:

1. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
2. Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.
3. Kirchheiner J et al. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. Clin Pharmacol Ther 2002;71:286-96.

Date 20-11-2017

CYP2C9*3/*3: glibenclamide **1881**

NO action is required for this gene-drug interaction.

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

Literature:

1. Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.
2. Kirchheiner J et al. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. Clin Pharmacol Ther 2002;71:286-96.

Date 20-11-2017

CYP2C9 IM: gliclazide **1889**

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:

1. Zeng W et al. CYP2C93 variant is associated with antidiabetes efficacy of gliclazide in Chinese type 2 diabetes patients. J Diabetes Investig 2016;7:764-8.
2. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
3. Zhou K et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther 2010;87:52-6.
4. Ragia G et al. Presence of CYP2C9*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. Pharmacogenomics 2009;10:1781-7.
5. Xu H et al. Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. Br J Pharmacol 2008;153:1579-86.
6. Zhang Y et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on pharmacokinetics of gliclazide MR in Chinese subjects. Br J Clin Pharmacol 2007;64:67-74.

Date 20-11-2017

CYP2C9 PM: gliclazide **1890**

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:

1. Zeng W et al. CYP2C93 variant is associated with antidiabetes efficacy of gliclazide in Chinese type 2 diabetes patients. J Diabetes Investig 2016;7:764-8.
2. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
3. Zhou K et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther 2010;87:52-6.
4. Xu H et al. Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. Br J Pharmacol 2008;153:1579-86.

Date 20-11-2017

CYP2C9*1/*2: gliclazide **1884**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide

Literature:

1. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
2. Zhou K et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther 2010;87:52-6.
3. Ragia G et al. Presence of CYP2C9*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. Pharmacogenomics 2009;10:1781-7.
4. Xu H et al. Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. Br J Pharmacol 2008;153:1579-86.

Date 20-11-2017

CYP2C9*1/*3: gliclazide **1885**

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:

1. Zeng W et al. CYP2C93 variant is associated with antidiabetes efficacy of gliclazide in Chinese type 2 diabetes patients. J Diabetes Investig 2016;7:764-8.
2. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
3. Zhou K et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther 2010;87:52-6.
4. Ragia G et al. Presence of CYP2C9*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. Pharmacogenomics 2009;10:1781-7.
5. Xu H et al. Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. Br J Pharmacol 2008;153:1579-86.
6. Zhang Y et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on pharmacokinetics of gliclazide MR in Chinese subjects. Br J Clin Pharmacol 2007;64:67-74.

Date 20-11-2017

CYP2C9*2/*2: gliclazide **1886**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide.

Literature:

1. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
2. Zhou K et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther 2010;87:52-6.
3. Xu H et al. Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. Br J Pharmacol 2008;153:1579-86.

Date 20-11-2017

CYP2C9*2/*3: gliclazide **1887**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of gliclazide.

Literature:

1. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
2. Zhou K et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther 2010;87:52-6.

Date 20-11-2017

CYP2C9*3/*3: gliclazide **1888**

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:

1. Zeng W et al. CYP2C93 variant is associated with antidiabetes efficacy of gliclazide in Chinese type 2 diabetes patients. J Diabetes Investig 2016;7:764-8.
2. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
3. Zhou K et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther 2010;87:52-6.

Date 20-11-2017

CYP2C9 IM: glimepiride **1896**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of glimepiride.

Literature:

1. Bhatt D et al. Investigating the role of plasma glucose concentration as a phenotypic marker for CYP2C9 genetic variants, in the diabetic population of Gujarat. Indian J Pharm Sci 2014;76:72-7.
2. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
3. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
4. Ragia G et al. Presence of CYP2C9*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. Pharmacogenomics 2009;10:1781-7.
5. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
6. Suzuki K et al. Effect of CYP2C9 genetic polymorphisms on the efficacy and pharmacokinetics of glimepiride in subjects with type 2 diabetes. Diabetes Res Clin Pract 2006;72:148-54.
7. Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.
8. Wang R et al. Pharmacokinetics of glimepiride and cytochrome P450 2C9 genetic polymorphisms. Clin Pharmacol Ther 2005;78:90-2.
9. Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.

Date 20-11-2017

CYP2C9 PM: glimepiride **1897**

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:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
3. Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.
4. Wang R et al. Pharmacokinetics of glimepiride and cytochrome P450 2C9 genetic polymorphisms. Clin Pharmacol Ther 2005;78:90-2.
5. Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.

Date 20-11-2017

CYP2C9*1/*2: glimepiride **1891**

NO action is required for this gene-drug interaction.

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

Literature:

1. Bhatt D et al. Investigating the role of plasma glucose concentration as a phenotypic marker for CYP2C9 genetic variants, in the diabetic population of Gujarat. Indian J Pharm Sci 2014;76:72-7.
2. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
3. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
4. Ragia G et al. Presence of CYP2C9*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. Pharmacogenomics 2009;10:1781-7.
5. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
6. Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.
7. Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.

Date 20-11-2017

CYP2C9*1/*3: glimepiride **1892**

NO action is required for this gene-drug interaction.

The genetic variation increases the effectiveness of glimepiride.

Literature:

1. Bhatt D et al. Investigating the role of plasma glucose concentration as a phenotypic marker for CYP2C9 genetic variants, in the diabetic population of Gujarat. Indian J Pharm Sci 2014;76:72-7.
2. Gökalp O et al. Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting. Eur J Clin Pharmacol 2011;67:1223-9.
3. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
4. Ragia G et al. Presence of CYP2C9*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. Pharmacogenomics 2009;10:1781-7.
5. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
6. Suzuki K et al. Effect of CYP2C9 genetic polymorphisms on the efficacy and pharmacokinetics of glimepiride in subjects with type 2 diabetes. Diabetes Res Clin Pract 2006;72:148-54.
7. Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.
8. Wang R et al. Pharmacokinetics of glimepiride and cytochrome P450 2C9 genetic polymorphisms. Clin Pharmacol Ther 2005;78:90-2.
9. Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.

Date 20-11-2017

CYP2C9*2/*2: glimepiride **1893**

NO action is required for this gene-drug interaction.

No significant clinical effects were observed for this genetic variation.

Literature:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.

Date 20-11-2017

CYP2C9*2/*3: glimepiride **1894**

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:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Becker ML et al. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
3. Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.
4. Niemi M et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002;72:326-32.

Date 20-11-2017

CYP2C9*3/*3: glimepiride **1895**

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:

1. Holstein A et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103-6.

2. Wang R et al. Pharmacokinetics of glimepiride and cytochrome P450 2C9 genetic polymorphisms. Clin Pharmacol Ther 2005;78:90-2.

Date 20-11-2017

CYP2D6 IM: haloperidol **1551**

NO action is required for this gene-drug interaction.

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

Literature:

1. Trogrlić Z et al. Pharmacogenomic response of low dose haloperidol in critically ill adults with delirium. J Crit Care 2020;57:203-7.
2. Sychev DA et al. The correlation between CYP2D6 isoenzyme activity and haloperidol efficacy and safety profile in patients with alcohol addiction during the exacerbation of the addiction. Pharmgenomics Pers Med 2016;9:89-95.
3. Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84.
4. 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).
5. Panagiotidis G et al. Depot haloperidol treatment in outpatients with schizophrenia on monotherapy: impact of CYP2D6 polymorphism on pharmacokinetics and treatment outcome. Ther Drug Monit 2007;29:417-22.
6. Park JY et al. Combined effects of itraconazole and CYP2D6*10 genetic polymorphism on the pharmacokinetics and pharmacodynamics of haloperidol in healthy subjects. J Clin Psychopharmacol 2006;26:135-42.
7. LLerena A et al. Relationship between haloperidol plasma concentration, debrisoquine metabolic ratio, CYP2D6 and CYP2C9 genotypes in psychiatric patients. Pharmacopsychiatry 2004;37:69-73.
8. Desai M et al. Pharmacokinetics and QT interval pharmacodynamics of oral haloperidol in poor and extensive metabolizers of CYP2D6. Pharmacogenomics J 2003;3:105-13.
9. Brockmoller J et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clin Pharmacol Ther 2002;72:438-52.
10. Yasui-Furukori N et al. Effect of the CYP2D6 genotype on prolactin concentration in schizophrenic patients treated with haloperidol. Schizophr Res 2001 1;52:139-42.
11. Pan L et al. Effects of smoking, CYP2D6 genotype, and concomitant drug intake on the steady state plasma concentrations of haloperidol and reduced haloperidol in schizophrenic inpatients. Ther Drug Monit 1999;21:489-97.
12. Llerena A et al. Haloperidol disposition is dependent on the debrisoquine hydroxylation phenotype: increased plasma levels of the reduced metabolite in poor metabolizers. Ther Drug Monit 1992;14:261-4.
13. Llerena A. Haloperidol disposition is dependent on debrisoquine hydroxylation phenotype. Ther Drug Monit 1992;14:92-7.

Date 14-09-2020

CYP2D6 PM: haloperidol **1552**

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:

1. Trogrlić Z et al. Pharmacogenomic response of low dose haloperidol in critically ill adults with delirium. J Crit Care 2020;57:203-7.
2. Šimić I et al. CYP2D6 *6*/6 genotype and drug interactions as cause of haloperidol-induced extrapyramidal symptoms. Pharmacogenomics 2016;17:1385-9.
3. Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84.
4. 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).
5. Butwicka A et al. Neuroleptic malignant syndrome in an adolescent with CYP2D6 deficiency. Eur J Pediatr 2014;173:1639-42.
6. Gassó P et al. Relationship between CYP2D6 genotype and haloperidol pharmacokinetics and extrapyramidal symptoms in healthy volunteers. Pharmacogenomics 2013;14:1551-63.
7. Panagiotidis G et al. Depot haloperidol treatment in outpatients with schizophrenia on monotherapy: impact of CYP2D6 polymorphism on pharmacokinetics and treatment outcome. Ther Drug Monit 2007;29:417-22.
8. LLerena A et al. Relationship between haloperidol plasma concentration, debrisoquine metabolic ratio, CYP2D6 and CYP2C9 genotypes in psychiatric patients. Pharmacopsychiatry 2004;37:69-73.
9. Desai M et al. Pharmacokinetics and QT interval pharmacodynamics of oral haloperidol in poor and extensive metabolizers of CYP2D6. Pharmacogenomics J 2003;3:105-13.
10. Brockmoller J et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clin Pharmacol Ther 2002;72:438-52.
11. Yasui-Furukori N et al. Effect of the CYP2D6 genotype on prolactin concentration in schizophrenic patients treated with haloperidol. Schizophr Res 2001 1;52:139-42.
12. Pan L et al. Effects of smoking, CYP2D6 genotype, and concomitant drug intake on the steady state plasma concentrations of haloperidol and reduced haloperidol in schizophrenic inpatients. Ther Drug Monit 1999;21:489-97.
13. Llerena A et al. Haloperidol disposition is dependent on the debrisoquine hydroxylation phenotype: increased plasma levels of the reduced metabolite in poor metabolizers. Ther Drug Monit 1992;14:261-4.
14. Llerena A. Haloperidol disposition is dependent on debrisoquine hydroxylation phenotype. Ther Drug Monit 1992;14:92-7.
15. SmPC's Haldol en Haldol Decanoas.

Date 14-09-2020

CYP2D6 UM: haloperidol **1553**

There are indications of a risk of reduced effectiveness. The genetic variation leads to an increased conversion of haloperidol, resulting in a 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:

1. Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84.
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).
3. Gassó P et al. Relationship between CYP2D6 genotype and haloperidol pharmacokinetics and extrapyramidal symptoms in healthy volunteers. Pharmacogenomics 2013;14:1551-63.
4. Panagiotidis G et al. Depot haloperidol treatment in outpatients with schizophrenia on monotherapy: impact of CYP2D6 polymorphism on pharmacokinetics and treatment outcome. Ther Drug Monit 2007;29:417-22.
5. Brockmoller J et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clin Pharmacol Ther 2002;72:438-52.

Date 09-11-2020

CYP2C19 IM: imipramine **1913**

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:

1. Schenk PW et al. The CYP2C19*17 genotype is associated with lower imipramine plasma concentrations in a large group of depressed patients. Pharmacogenomics J 2010;10:219-25.
2. Schenk PW et al. Association of graded allele-specific changes in CYP2D6 function with imipramine dose requirement in a large group of depressed patients. Mol Psychiatry 2008;13:597-605.
3. Madsen H et al. Imipramine demethylation in vivo: impact of CYP1A2, CYP2C19, and CYP3A4. Clin Pharmacol Ther 1997;61:319-24.
4. Koyama E et al. Steady-state plasma concentrations of imipramine and desipramine in relation to S-mephenytoin 4-hydroxylation status in Japanese depressive patients. J Clin Psychopharmacol 1996;16:286-93.
5. Madsen H et al. Imipramine metabolism in relation to the sparteine and mephenytoin oxidation polymorphisms--a population study. Br J Clin Pharmacol 1995;39:433-9.
6. Koyama E et al. Metabolic disposition of imipramine in oriental subjects: relation to metoprolol alpha-hydroxylation and S-mephenytoin 4-hydroxylation phenotypes. J Pharmacol Exp Ther 1994;271:860-7.
7. Skjelbo E et al. The N-demethylation of imipramine correlates with the oxidation of S-mephenytoin (S/R-ratio). A population study. Br J Clin Pharmacol 1993;35:331-4.

Date 10-09-2018

CYP2C19 PM: imipramine **1914**

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:

1. Schenk PW et al. The CYP2C19*17 genotype is associated with lower imipramine plasma concentrations in a large group of depressed patients. Pharmacogenomics J 2010;10:219-25.
2. Schenk PW et al. Association of graded allele-specific changes in CYP2D6 function with imipramine dose requirement in a large group of depressed patients. Mol Psychiatry 2008;13:597-605.
3. Morinobu S et al. Effects of genetic defects in the CYP2C19 gene on the N-demethylation of imipramine, and clinical outcome of imipramine therapy. Psychiatry Clin Neurosci 997;51:253-7.
4. Madsen H et al. Imipramine demethylation in vivo: impact of CYP1A2, CYP2C19, and CYP3A4. Clin Pharmacol Ther 1997;61:319-24.
5. Koyama E et al. Steady-state plasma concentrations of imipramine and desipramine in relation to S-mephenytoin 4-hydroxylation status in Japanese depressive patients. J Clin Psychopharmacol 1996;16:286-93.
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Date 10-09-2018

CYP2C19 UM: imipramine **1915**

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:

1. Schenk PW et al. The CYP2C19*17 genotype is associated with lower imipramine plasma concentrations in a large group of depressed patients. Pharmacogenomics J 2010;10:219-25.

Date 10-09-2018

CYP2D6 IM: imipramine **1545**

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:

1. Schliessbach J et al. Effect of single-dose imipramine on chronic low-back and experimental pain. A randomized controlled trial. PLoS One 2018;13:e0195776.
2. Schenk PW et al. Association of graded allele-specific changes in CYP2D6 function with imipramine dose requirement in a large group of depressed patients. Mol Psychiatry 2008;13:597-605.
3. Sindrup SH et al. Nonlinear kinetics of imipramine in low and medium plasma level ranges. Ther Drug Monit 1990;12:445-9.
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Date 19-11-2018

CYP2D6 PM: imipramine **1544**

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:

1. Schenk PW et al. Association of graded allele-specific changes in CYP2D6 function with imipramine dose requirement in a large group of depressed patients. Mol Psychiatry 2008;13:597-605.
2. Koyama E et al. Metabolic disposition of imipramine in oriental subjects: relation to metoprolol alpha-hydroxylation and S-mephenytoin 4"-hydroxylation phenotypes. J Pharmacol Exp Ther 1994;271:860-7.
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4. Balant-Gorgia AE et al. High blood concentrations of imipramine or clomipramine and therapeutic failure: a case report study using drug monitoring data. Ther Drug Monit 1989;11:415-20.
5. Brosen K et al. Imipramine demethylation and hydroxylation: impact of the sparteine oxidation phenotype. Clin Pharmacol Ther 1986;40:543-9.
6. Brosen K et al. Steady-state concentrations of imipramine and its metabolites in relation to the sparteine/debrisoquine polymorphism. Eur J Clin Pharmacol 1986;30:679-84.
7. SmPC Tofranil-PM (VS).

Date 19-11-2018

CYP2D6 UM: imipramine **1546**

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

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

Literature:

1. Schenk PW et al. Association of graded allele-specific changes in CYP2D6 function with imipramine dose requirement in a large group of depressed patients. Mol Psychiatry 2008;13:597-605.
2. Sindrup SH et al. Nonlinear kinetics of imipramine in low and medium plasma level ranges. Ther Drug Monit 1990;12:445-9.

Date 19-11-2018

UGT1A1 *1/*28: irinotecan **1693**

NO action is needed for this gene-drug interaction.

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

Literature:

1. 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.
2. Liu XH et al. Predictive value of UGT1A1*28 polymorphism in irinotecan-based chemotherapy. J Cancer 2017;8:691-703.
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4. Chen YJ et al. The association of UGT1A1*6 and UGT1A1*28 with irinotecan-induced neutropenia in Asians: a meta-analysis. Biomarkers. 2014;19:56-62.
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10. Hu ZY et al. Dose-dependent association between UGT1A1*28 polymorphism and irinotecan-induced diarrhoea: a meta-analysis. Eur J Cancer 2010;46:1856-65.
11. Denlinger CS et al. Pharmacokinetic analysis of irinotecan plus bevacizumab in patients with advanced solid tumors. Cancer Chemother Pharmacol 2009;65:97-105.Kweekel DM et al. UGT1A1*28 genotype and irinotecan dosage in patients with metastatic colorectal cancer: a Dutch Colorectal Cancer Group study. Br J Cancer 2008;99:275-82.
12. Liu CY et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer 2008;112:1932-40.
13. Lankisch TO et al. Gilbert's Syndrome and irinotecan toxicity: combination with UDP-glucuronosyl-transferase 1A7 variants increases risk. Cancer Epidemiol Biomarkers Prev 2008;17:695-701.
14. Minami H et al. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and 28. Pharmacogenet Genomics 2007;17:497-504.
15. Stewart CF et al. UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. J Clin Oncol 2007;25:2594-600.
16. Côté JF et al. UGT1A1 polymorphism can predict hematologic toxicity in patients treated with irinotecan. Clin Cancer Res 2007;13:3269-75.
17. Ramchandani RP et al. The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. J Clin Pharmacol 2007;47:78-86.
18. Zárate Romero R et al. Potential application of GSTT1-null genotype in predicting toxicity associated to 5-fluouracil irinotecan and leucovorin regimen in advanced stage colorectal cancer patients. Oncol Rep 2006;16:497-503.
19. de Jong FA et al. Prophylaxis of irinotecan-induced diarrhea with neomycin and potential role for UGT1A1*28 genotype screening: a double-blind, randomized, placebo-controlled study. Oncologist 2006;11:944-54.
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36. Iyer L et al. UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002;2:43-7.
37. Ando Y et al. Polymorphisms of UDP-glucuronosyl-transferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 2000;60:6921-6.
38. Wasserman E et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. Ann Oncol 1997;8:1049-51.

Date 05-03-2018

UGT1A1 *28/*28: irinotecan **1694**

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. 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.
2. Liu XH et al. Predictive value of UGT1A1*28 polymorphism in irinotecan-based chemotherapy. J Cancer 2017;8:691-703.
3. Lu CY et al. Clinical implication of UGT1A1 promoter polymorphism for irinotecan dose escalation in metastatic colorectal cancer patients treated with bevacizumab combined with FOLFIRI in the first-line setting. Transl Oncol 2015;8:474-9.
4. Dias MM et al. The effect of the UGT1A1*28 allele on survival after irinotecan-based chemotherapy: a collaborative meta-analysis. Pharmacogenomics J 2014;14:424-31.
5. Han FF et al. Associations between UGT1A1*6 or UGT1A16/*28 polymorphisms and irinotecan-induced neutropenia in Asian cancer patients. Cancer Chemother Pharmacol 2014;73:779-88.
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18. Minami H et al. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and* 28. Pharmacogenet Genomics 2007;17:497-504.
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29. Carlini LE et al. UGT1A7 and UGT1A9 polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/ irinotecan. Clin Cancer Res 2005;11:1226-36.
30. Kitagawa C et al. Genetic polymorphism in the phenobarbital-responsive enhancer module of the UDP-glucuronosyltransferase 1A1 gene and irinotecan toxicity. Pharmacogenet Genomics 2005;15:35-41.
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33. Paoluzzi L et al. Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. J Clin Pharmacol 2004;44:854-60.
34. Sai K et al. UGT1A1 haplotypes associated with reduced glucuronidation and increased serum bilirubin in irinotecan-administered Japanese patients with cancer. Clin Pharmacol Ther 2004;75:501-15.
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39. Ando Y et al. Polymorphisms of UDP-glucuronosyl-transferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 2000;60:6921-6.
40. Wasserman E et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. Ann Oncol 1997;8:1049-51.
41. SPC's Campto en Camptosar (VS).

Date 05-03-2018

UGT1A1 IM: irinotecan **1691**

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. 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.
2. Chen YJ et al. The association of UGT1A1*6 and UGT1A1*28* with irinotecan-induced neutropenia in Asians: a meta-analysis. Biomarkers. 2014;19:56-62.
3. Goetz MP et al. UGT1A1 genotype-guided phase I study of irinotecan, oxaliplatin, and capecitabine. Invest New Drugs 2013;31:1559-67.
4. Denlinger CS et al. Pharmacokinetic analysis of irinotecan plus bevacizumab in patients with advanced solid tumors. Cancer Chemother Pharmacol 2009;65:97-105.
5. Minami H et al. Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and* 28. Pharmacogenet Genomics 2007;17:497-504.
6. de Jong FA et al. Prophylaxis of irinotecan-induced diarrhea with neomycin and potential role for UGT1A1*28 genotype screening: a double-blind, randomized, placebo-controlled study. Oncologist 2006;11:944-54.
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8. Paoluzzi L et al. Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. J Clin Pharmacol 2004;44:854-60.
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Date 05-03-2018

UGT1A1 PM: irinotecan **1692**

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. 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.
2. Han FF et al. Associations between UGT1A1*6 or UGT1A16*/*28 polymorphisms and irinotecan-induced neutropenia in Asian cancer patients. Cancer Chemother Pharmacol 2014;73:779-88.
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10. Paoluzzi L et al. Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. J Clin Pharmacol 2004;44:854-60.
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Date 05-03-2018

CYP2D6 IM: kinidine **2534**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2D6 PM: kinidine **2533**

This is NOT a gene-drug interaction.

Literature:

1. Nielsen F et al. Lack of relationship between quinidine pharmacokinetics and the sparteine oxidation polymorphism. Eur J Clin Pharmacol 1995;48:501-4.
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Date 24-08-2016

CYP2D6 UM: kinidine **2535**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2C19 IM: lansoprazol **1831**

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:

1. Lang JE et al. Lansoprazole is associated with worsening asthma control in children with the CYP2C19 poor metabolizer phenotype. Ann Am Thorac Soc 2015 Jun;12:878-85.
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Date 05-03-2018

CYP2C19 PM: lansoprazol **1832**

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:

1. Liou JM et al. Sequential therapy for 10 days versus triple therapy for 14 days in the eradication of Helicobacter pylori in the community and hospital populations: a randomised trial. Gut 2016;65:1784-1792.
2. Liou JM et al. Levofloxacin sequential therapy vs levofloxacin triple therapy in the second-line treatment of Helicobacter pylori: a randomized trial. Am J Gastroenterol 2016;111:381-7.
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39. SPC Prezal.

Date 05-03-2018

CYP2C19 UM: lansoprazol **1833**

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:

1. Liou JM et al. Sequential therapy for 10 days versus triple therapy for 14 days in the eradication of Helicobacter pylori in the community and hospital populations: a randomised trial. Gut 2016;65:1784-1792.
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41. SPC Prezal.

Date 05-03-2018

CYP2D6 IM: methylfenidaat **2528**

This is NOT a gene-drug interaction.

Literature:
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Date 24-08-2016

CYP2D6 PM: methylfenidaat **2527**

This is NOT a gene-drug interaction.

Literature:

1. DeVane CL et al. Single-dose pharmacokinetics of methylphenidate in CYP2D6 extensive and poor metabolizers. J Clin Psychopharmacol 2000;20:347-9.

Date 24-08-2016

CYP2D6 UM: methylfenidaat **2529**

This is NOT a gene-drug interaction.

Literature:
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Date 24-08-2016

CYP2D6 IM: metoprolol **1554**

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. increase the dose in smaller steps and/or prescribe no more than 50% of the standard dose
- OTHER CASES:
  1. no action required

Literature:

1. Hamadeh IS et al. Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate. Clin Pharmacol Ther 2014;96:175-81.
2. Batty JA et al. An investigation of CYP2D6 genotype and response to metoprolol CR/XL during dose titration in patients with heart failure: a MERIT-HF substudy. Clin Pharmacol Ther 2014;95:321-30.
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Date 25-05-2016

CYP2D6 PM: metoprolol **1555**

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. increase the dose in smaller steps and/or prescribe no more than 25% of the standard dose
- OTHER CASES:
  1. no action required

Literature:

1. Hamadeh IS et al. Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate. Clin Pharmacol Ther 2014;96:175-81.
2. Batty JA et al. An investigation of CYP2D6 genotype and response to metoprolol CR/XL during dose titration in patients with heart failure: a MERIT-HF substudy. Clin Pharmacol Ther 2014;95:321-30.
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Date 25-05-2016

CYP2D6 UM: metoprolol **1556**

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

Recommendation:

1. use the maximum dose for the relevant indication as a target dose
2. if the effectiveness is still insufficient: increase the dose based on effectiveness and side effects to 2.5 times the standard dose or select an alternative
   Possible alternatives include:
   - HEART FAILURE: bisoprolol or carvedilol. Bisoprolol: advantage: not metabolised by CYP2D6; disadvantage: elimination depends on the kidney function. Carvedilol: advantage: elimination does not depend on the kidney function; disadvantage: is metabolised (to a lesser extent than metoprolol) by CYP2D6.
   - OTHER INDICATIONS: atenolol or bisoprolol. Neither is metabolised by CYP2D6.

Literature:

1. Hamadeh IS et al. Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate. Clin Pharmacol Ther 2014;96:175-81.
2. Goryachkina K et al. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. Eur J Clin Pharmacol 2008;64:1163-73.
3. Seeringer A et al. Enantiospecific pharmacokinetics of metoprolol in CYP2D6 ultra-rapid metabolizers and correlation with exercise-induced heart rate. Eur J Clin Pharmacol 2008;64:883-8.
4. Ismail R et al. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. J Clin Pharm Ther 2006;31:99-109.
5. Fux R et al. Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. Clin Pharmacol Ther 2005;78:378-87.
6. Kirchheiner J et al. Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 2004;76:302-12.

Date 25-05-2016

CYP2C19 IM: mirtazapine **3507**

This is NOT a gene-drug interaction.

Literature:

1. Grasmäder K et al. Population pharmacokinetic analysis of mirtazapine. Eur J Clin Pharmacol 2004;60:473-80.

Date 10-09-2018

CYP2C19 PM: mirtazapine **3506**

This is NOT a gene-drug interaction.

Literature:

1. Johnson M et al. A poor metabolizer for cytochromes P450 2D6 and 2C19: a case report on antidepressant treatment. CNS Spectr 2006;11:757-60.

Date 10-09-2018

CYP2C19 UM: mirtazapine **3508**

This is NOT a gene-drug interaction.

Literature:

1. Grasmäder K et al. Population pharmacokinetic analysis of mirtazapine. Eur J Clin Pharmacol 2004;60:473-80.

Date 10-09-2018

CYP2D6 IM: mirtazapine **2002**

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:

1. Zastrozhin MS et al. Effects of CYP2D6 activity on the efficacy and safety of mirtazapine in patients with depressive disorders and comorbid alcohol use disorder. Can J Physiol Pharmacol 2019;97:781-5.
2. Hayashi Y et al. Factors affecting steady-state plasma concentrations of enantiomeric mirtazapine and its desmethylated metabolites in Japanese psychiatric patients. Pharmacopsychiatry 2015;48:279-85.
3. Okubo M et al. Effects of cytochrome P450 2D6 and 3A5 genotypes and possible coadministered medicines on the metabolic clearance of antidepressant mirtazapine in Japanese patients. Biochem Pharmacol 2015;93:104-9.
4. Jaquenoud Sirot E et al. Multicenter study on the clinical effectiveness, pharmacokinetics, and pharmacogenetics of mirtazapine in depression. J Clin Psychopharmacol 2012;32:622-9.
5. Borobia AM et al. Influence of sex and CYP2D6 genotype on mirtazapine disposition, evaluated in Spanish healthy volunteers. Pharmacol Res 2009;59:393-8.
6. Lind AB et al. Steady-state concentrations of mirtazapine, N-desmethylmirtazapine, 8-hydroxymirtazapine and their enantiomers in relation to cytochrome P450 2D6 genotype, age and smoking behaviour. Clin Pharmacokinet 2009;48:63-70.
7. Grasmader K et al. Population pharmacokinetic analysis of mirtazapine. Eur J Clin Pharmacol 2004;60:473-80.
8. Murphy GM Jr et al. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003;160:1830-5.

Date 18-05-2020

CYP2D6 PM: mirtazapine **2001**

NO action is required for this gene-drug interaction.

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

Literature:

1. Jaquenoud Sirot E et al. Multicenter study on the clinical effectiveness, pharmacokinetics, and pharmacogenetics of mirtazapine in depression. J Clin Psychopharmacol 2012;32:622-9.
2. Ramaekers JG et al. Residual effects of esmirtazapine on actual driving performance: overall findings and an exploratory analysis into the role of CYP2D6 phenotype. Psychopharmacology 2011;215:321-32.
3. Borobia AM et al. Influence of sex and CYP2D6 genotype on mirtazapine disposition, evaluated in Spanish healthy volunteers. Pharmacol Res 2009;59:393-8.
4. Lind AB et al. Steady-state concentrations of mirtazapine, N-desmethylmirtazapine, 8-hydroxymirtazapine and their enantiomers in relation to cytochrome P450 2D6 genotype, age and smoking behaviour. Clin Pharmacokinet 2009;48:63-70.
5. Brockmoller J et al. Pharmacokinetics of mirtazapine: enantioselective effects of the CYP2D6 ultra rapid metabolizer genotype and correlation with adverse effects. Clin Pharmacol Ther 2007;81:699-707.
6. Johnson M et al. A poor metabolizer for cytochromes P450 2D6 and 2C19: a case report on antidepressant treatment. CNS Spectr 2006;11:757-60.
7. Stephan PL et al. Adverse drug reactions following nonresponse in a depressed patient with CYP2D6 deficiency and low CYP 3A4/5 activity. Pharmacopsychiatry 2006;39:150-2.
8. Kirchheiner J et al. Impact of the CYP2D6 ultrarapid metabolizer genotype on mirtazapine pharmacokinetics and adverse events in healthy volunteers. J Clin Psychopharmacol 2004;24:647-52.
9. Grasmader K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.
10. Murphy GM Jr et al. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003;160:1830-5.

Date 18-05-2020

CYP2D6 UM: mirtazapine **2003**

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:

1. Jaquenoud Sirot E et al. Multicenter study on the clinical effectiveness, pharmacokinetics, and pharmacogenetics of mirtazapine in depression. J Clin Psychopharmacol 2012;32:622-9.
2. Lind AB et al. Steady-state concentrations of mirtazapine, N-desmethylmirtazapine, 8-hydroxymirtazapine and their enantiomers in relation to cytochrome P450 2D6 genotype, age and smoking behaviour. Clin Pharmacokinet 2009;48:63-70.
3. Brockmoller J et al. Pharmacokinetics of mirtazapine: enantioselective effects of the CYP2D6 ultra rapid metabolizer genotype and correlation with adverse effects. Clin Pharmacol Ther 2007;81:699-707.
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5. Grasmader K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.

Date 18-05-2020

CYP2C19 IM: moclobemide **1991**

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, in as far as is known.

Literature:

1. Gram LF et al. Moclobemide, a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2: a panel study. Clin Pharmacol Ther 1995;57:670-7.
2. SPC Aurorix.

Date 04-03-2019

CYP2C19 PM: moclobemide **1992**

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, in as far as is known.

Literature:

1. Yu KS et al. Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. Clin Pharmacol Ther 2001;69:266-73.
2. Gram LF et al. Moclobemide, a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2: a panel study. Clin Pharmacol Ther 1995;57:670-7.
3. SPC Aurorix.

Date 04-03-2019

CYP2C19 UM: moclobemide **1993**

NO action is needed for this gene-drug interaction.

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

Literature:

1. Gram LF et al. Moclobemide, a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2: a panel study. Clin Pharmacol Ther 1995;57:670-7.
2. SPC Aurorix.

Date 04-03-2019

CYP2D6 IM: nortriptyline **1557**

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:

1. Berm E et al. Relation between CYP2D6 genotype, phenotype and therapeutic drug concentrations among nortriptyline and venlafaxine users in old age psychiatry. Pharmacopsychiatry 2016;49:186-190.
2. Hodgson K et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl) 2015;232:2609-17.
3. Hodgson K et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. J Psychopharmacol 2014;28:133-41.
4. Lee SY et al. Sequence-based CYP2D6 genotyping in the Korean population. Ther Drug Monit 2006;28:382-7.
5. Lee S et al. A case report of a poor metabolizer of CYP2D6 presented with unusual responses to nortriptyline medication. J Korean Med Sci 2004;19:750-2.
6. Dalen P et al. Disposition of debrisoquine and nortriptyline in Korean subjects in relation to CYP2D6 genotypes, and comparison with Caucasians. Br J Clin Pharmacol 2003;55:630-4.
7. Kvist EE et al. Quantitative pharmacogenetics of nortriptyline: a novel approach. Clin Pharmacokinet 2001;40:869-77.
8. Morita S et al. Steady-state plasma levels of nortriptyline and its hydroxylated metabolites in Japanese patients: impact of CYP2D6 genotype on the hydroxylation of nortriptyline. J Clin Psychopharmacol 2000;20:141-9.
9. Yue QJ et al. Pharmacokinetics of nortriptyline and its 10-hydroxymetabolite in Chinese subjects of different CYP2D6 genotypes. Clin Pharmacol Ther 1998;64:384-90.
10. Chen S et al. The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry. Clin Pharmacol Ther 1996;60:522-34.

Date 19-11-2018

CYP2D6 PM: nortriptyline **1558**

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:

1. Berm E et al. Relation between CYP2D6 genotype, phenotype and therapeutic drug concentrations among nortriptyline and venlafaxine users in old age psychiatry. Pharmacopsychiatry 2016;49:186-190.
2. Hodgson K et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl) 2015;232:2609-17.
3. Hodgson K et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. J Psychopharmacol 2014;28:133-41.
4. Roberts et al. No evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolizers treated with fluoxetine or nortriptyline. Hum Psychopharmacol 2004 Jan;19:17-23.
5. Kvist EE et al. Quantitative pharmacogenetics of nortriptyline: a novel approach. Clin Pharmacokinet 2001;40:869-77.
6. Dalen P et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. Clin Pharmacol Ther 1998;63:444-52.
7. Dahl M et al. Steady-state plasma levels of nortriptyline and its 10-hydroxymetabolite: relationship to the CYP2D6 genotype. Psychopharmacol 1996;123:315-9.
8. Chen S et al. The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry. Clin Pharmacol Ther 1996;60:522-34.
9. Bertilsson L et al. Slow hydroxylation of nortriptyline and concomitant poor debrisoquine hydroxylation: clinical implications. Lancet 1981;1:560-1.
10. SmPC Pamelor (VS).

Date 19-11-2018

CYP2D6 UM: nortriptyline **1559**

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

- use 1.7 times the standard dose and monitor the effect and side effects or the plasma concentration of nortriptyline and be alert to an increase in the plasma concentration of the cardiotoxic metabolite Z-10-hydroxynortriptyline
  Plasma concentrations of Z-hydroxynortriptyline exceeding 40 ng/mL are considered toxic.
- if a dose increase is not wanted due to the cardiotoxic hydroxy metabolite: avoid nortriptyline
  Antidepressants that are not metabolised via CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.

Literature:

1. Hodgson K et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl) 2015;232:2609-17.
2. Hodgson K et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. J Psychopharmacol 2014;28:133-41.
3. Lee SY et al. Sequence-based CYP2D6 genotyping in the Korean population. Ther Drug Monit 2006;28:382-7.
4. Kvist EE et al. Quantitative pharmacogenetics of nortriptyline: a novel approach. Clin Pharmacokinet 2001;40:869-77.
5. Dalen P et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. Clin Pharmacol Ther 1998;63:444-52.
6. Bertilsson L et al. Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine. Lancet 1993;341:63.

Date 19-11-2018

CYP2D6 IM: olanzapine **1560**

This is NOT a gene-drug interaction.

Literature:

1. Koller D et al. The effects of aripiprazole and olanzapine on pupillary light reflex and its relationship with pharmacogenetics in a randomized multiple-dose trial. Br J Clin Pharmacol 2020;86:2051-62, and personal communication (supplementary files).
2. Miroshnichenko II et al. Therapeutic drug monitoring of olanzapine and cytochrome P450 genotyping in nonsmoking subjects. Ther Drug Monit 2020;42:325-9.
3. Djordjevic N et al. Cigarette smoking and heavy coffee consumption affecting response to olanzapine: The role of genetic polymorphism. World J Biol Psychiatry 2020;21:29-52.
4. Okubo M et al. Individual differences in in vitro and in vivo metabolic clearances of the antipsychotic drug olanzapine from non-smoking and smoking Japanese subjects genotyped for cytochrome P4502D6 and flavincontaining monooxygenase 3. Hum Psychopharmacol 2016;31:83-92.
5. Cabaleiro T et al. Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects. Hum Psychopharmacol 2013;28:205-14.
6. Thomas P et al. Correlates of response to olanzapine in a North Indian schizophrenia sample. Psychiatry Res 2008;161:275-83.
7. Nozawa M et al. The relationship between the response of clinical symptoms and plasma olanzapine concentration, based on pharmacogenetics: Juntendo University Schizophrenia Projects (JUSP). Ther Drug Monit 2008;30:35-40.
8. Iwahashi K. Olanzapine metabolism by CYP1A2/CYP2D6 and hyperglycaemia. Acta Neuropsychiatrica 2004;16:229-230.

Date 09-11-2020

CYP2D6 PM: olanzapine **1561**

This is NOT a gene-drug interaction.

Literature:

1. Djordjevic N et al. Cigarette smoking and heavy coffee consumption affecting response to olanzapine: The role of genetic polymorphism. World J Biol Psychiatry 2020;21:29-52.
2. Cabaleiro T et al. Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects. Hum Psychopharmacol 2013;28:205-14.
3. Skogh E et al. High correlation between serum and cerebrospinal fluid olanzapine concentrations in patients with schizophrenia or schizoaffective disorder medicating with oral olanzapine as the only antipsychotic drug. J Clin Psychopharmacol 2011;31:4-9.
4. Thomas P et al. Correlates of response to olanzapine in a North Indian schizophrenia sample. Psychiatry Res 2008;161:275-83.
5. Carrillo JA et al. Role of the smoking-induced cytochrome P450 (CYP)1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine. J Clin Psychopharmacol 2003;23:119-27.
6. Hagg S et al. Olanzapine disposition in humans is unrelated to CYP1A2 and CYP2D6 phenotypes. Eur J Clin Pharmacol 2001;57:493-7.

Date 09-11-2020

CYP2D6 UM: olanzapine **1562**

This is NOT a gene-drug interaction.

Literature:

1. Koller D et al. The effects of aripiprazole and olanzapine on pupillary light reflex and its relationship with pharmacogenetics in a randomized multiple-dose trial. Br J Clin Pharmacol 2020;86:2051-62, and personal communication (supplementary files).
2. Cabaleiro T et al. Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects. Hum Psychopharmacol 2013;28:205-14.
3. Skogh E et al. High correlation between serum and cerebrospinal fluid olanzapine concentrations in patients with schizophrenia or schizoaffective disorder medicating with oral olanzapine as the only antipsychotic drug. J Clin Psychopharmacol 2011;31:4-9.

Date 09-11-2020

CYP2C19 IM: omeprazol **1839**

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:

1. Park S et al. Effects of CYP2C19 genetic polymorphisms on PK/PD responses of omeprazole in Korean healthy volunteers. J Korean Med Sci 2017;32:729-736.
2. Tang HL et al. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. PLoS One 2013;8:e62162.
3. Wang L et al. Ilaprazole for the treatment of duodenal ulcer: a randomized, double-blind and controlled phase III trial. Curr Med Res Opin 2012;28:101-9.
4. Zendehdel N et al. Role of cytochrome P450 2C19 genetic polymorphisms in the therapeutic efficacy of omeprazole in Iranian patients with erosive reflux esophagitis. Arch Iran Med 2010;13:406-12.
5. Helsby NA et al. Omeprazole-induced acute interstitial nephritis is not related to CYP2C19 genotype or CYP2C19 phenotype. Br J Clin Pharmacol 2010;69:516-9.
6. Saitoh T et al. Influences of CYP2C19 polymorphism on recurrence of reflux esophagitis during proton pump inhibitor maintenance therapy. Hepatogastroenterology 2009;56:703-6.
7. Hunfeld NG et al. Effect of CYP2C19*2 and* 17 mutations on pharmacodynamics and kinetics of proton pump inhibitors in Caucasians. Br J Clin Pharmacol 2008;65:752-60.
8. Ohkusa T et al. Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux esophagitis. Aliment Pharmacol Ther 2005;21:1331-9.
9. Roh HK et al. Omeprazole treatment of Korean patients: effects on gastric pH and gastrin release in relation to CYP2C19 geno- and phenotypes. Basic Clin Pharmacol Toxicol 2004;95:112-9.
10. Shirai N et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. Aliment Pharmacol Ther 2001;15:1929-37.
11. Sagar M et al. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism. Gastroenterology 2000;119:670-6.
12. Furuta T et al. CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. Clin Pharmacol Ther 1999;65:552-61.
13. Shimatani T et al. Effect of omeprazole 10 mg on intragastric pH in three different CYP2C19 genotypes, compared with omeprazole 20 mg and lafutidine 20 mg, a new H2-receptor antagonist. Aliment Pharmacol Ther 2003;18:1149–1157.
14. Ando T et al. Endoscopic analysis of gastric ulcer after one week's treatment with omeprazole and rabeprazole in relation to CYP2C19 genotype. Dig Dis Sci 2008;53:933-7.
15. Sugimoto M et al. Initial 48-hour acid inhibition by intravenous infusion of omeprazole, famotidine, or both in relation to cytochrome P450 2C19 genotype status. Clin Pharmacol Ther 2006;80:539-48.
16. Ando T et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. Dig Dis Sci 2005;50:1625-31.
17. Zhao F et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter 2008;13:532-41.
18. Sugimoto M et al. Influences of proinflammatory and anti-inflammatory cytokine polymorphisms on eradication rates of clarithromycin-sensitive strains of Helicobacter pylori by triple therapy. Clin Pharmacol Ther 2006;80:41-50.
19. Gawronska-Szklarz B et al. Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders with Helicobacter pylori infection. Eur J Clin Pharmacol 2005;61:375-9.
20. Sheu BS et al. Esomeprazole 40 mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to CYP2C19 metabolism. Aliment Pharmacol Ther 2005;21:283-8.
21. Furuta T et al. Polymorphism of interleukin-1beta affects the eradication rates of Helicobacter pylori by triple therapy. Clin Gastroenterol Hepatol 2004;2:22-30.
22. Sapone A et al. The clinical role of cytochrome p450 genotypes in Helicobacter pylori management. Am J Gastroenterol 2003;98:1010-5.
23. Miwa H et al. Clarithromycin resistance, but not CYP2C-19 polymorphism, has a major impact on treatment success in 7-day treatment regimen for cure of H. pylori infection: a multiple logistic regression analysis. Dig Dis Sci 2001;46:2445-50.
24. Dojo M et al. Effects of CYP2C19 gene polymorphism on cure rates for Helicobacter pylori infection by triple therapy with proton pump inhibitor (omeprazole or rabeprazole), amoxycillin and clarithromycin in Japan. Dig Liver Dis 2001;33:671-5.
25. Furuta T et al. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin Pharmacol Ther 2001;69:158-68.
26. Aoyama N et al. Sufficient effect of 1-week omeprazole and amoxicillin dual treatment for Helicobacter pylori eradication in cytochrome P450 2C19 poor metabolizers. J Gastroenterol 1999;34 Suppl 11:80-3.
27. Inaba T et al. Helicobacter pylori infection: CYP2C19 genotype and serum ferritin. J Gastroenterol Hepatol 2002;17:748-53.
28. Hu XP et al. Effects of CYP2C19 genetic polymorphism on the pharmacokinetics and pharmacodynamics of omeprazole in Chinese people. J Clin Pharm Ther 2007;32:517-24.
29. SmPC Prilosec (VS).

Date 05-03-2018

CYP2C19 PM: omeprazol **1840**

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:

1. Park S et al. Effects of CYP2C19 genetic polymorphisms on PK/PD responses of omeprazole in Korean healthy volunteers. J Korean Med Sci 2017;32:729-736.
2. Tang HL et al. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. PLoS One 2013;8:e62162.
3. Wang L et al. Ilaprazole for the treatment of duodenal ulcer: a randomized, double-blind and controlled phase III trial. Curr Med Res Opin 2012;28:101-9.
4. Helsby NA et al. Omeprazole-induced acute interstitial nephritis is not related to CYP2C19 genotype or CYP2C19 phenotype. Br J Clin Pharmacol 2010;69:516-9.
5. Saitoh T et al. Influences of CYP2C19 polymorphism on recurrence of reflux esophagitis during proton pump inhibitor maintenance therapy. Hepatogastroenterology 2009;56:703-6.
6. Ohkusa T et al. Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux esophagitis. Aliment Pharmacol Ther 2005;21:1331-9.
7. Roh HK et al. Omeprazole treatment of Korean patients: effects on gastric pH and gastrin release in relation to CYP2C19 geno- and phenotypes. Basic Clin Pharmacol Toxicol 2004;95:112-9.
8. Shirai N et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. Aliment Pharmacol Ther 2001;15:1929-37.
9. Sagar M et al. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism. Gastroenterology 2000;119:670-6.
10. Furuta T et al. CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. Clin Pharmacol Ther 1999;65:552-61.
11. Shimatani T et al. Effect of omeprazole 10 mg on intragastric pH in three different CYP2C19 genotypes, compared with omeprazole 20 mg and lafutidine 20 mg, a new H2-receptor antagonist. Aliment Pharmacol Ther 2003;18:1149–1157.
12. Ando T et al. Endoscopic analysis of gastric ulcer after one week's treatment with omeprazole and rabeprazole in relation to CYP2C19 genotype. Dig Dis Sci 2008;53:933-7.
13. Sugimoto M et al. Initial 48-hour acid inhibition by intravenous infusion of omeprazole, famotidine, or both in relation to cytochrome P450 2C19 genotype status. Clin Pharmacol Ther 2006;80:539-48.
14. Ji S et al. Comparison of the efficacy of rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of peptic ulcer diseases. J Gastroenterol Hepatol 2006;21:1381-7.
15. Ando T et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. Dig Dis Sci 2005;50:1625-31.
16. Zhao F et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter 2008;13:532-41.
17. Sugimoto M et al. Influences of proinflammatory and anti-inflammatory cytokine polymorphisms on eradication rates of clarithromycin-sensitive strains of Helicobacter pylori by triple therapy. Clin Pharmacol Ther 2006;80:41-50.
18. Sheu BS et al. Esomeprazole 40 mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to CYP2C19 metabolism. Aliment Pharmacol Ther 2005;21:283-8.
19. Furuta T et al. Polymorphism of interleukin-1beta affects the eradication rates of Helicobacter pylori by triple therapy. Clin Gastroenterol Hepatol 2004;2:22-30.
20. Sapone A et al. The clinical role of cytochrome p450 genotypes in Helicobacter pylori management. Am J Gastroenterol 2003;98:1010-5.
21. Miwa H et al. Clarithromycin resistance, but not CYP2C-19 polymorphism, has a major impact on treatment success in 7-day treatment regimen for cure of H. pylori infection: a multiple logistic regression analysis. Dig Dis Sci 2001;46:2445-50.
22. Dojo M et al. Effects of CYP2C19 gene polymorphism on cure rates for Helicobacter pylori infection by triple therapy with proton pump inhibitor (omeprazole or rabeprazole), amoxycillin and clarithromycin in Japan. Dig Liver Dis 2001;33:671-5.
23. Furuta T et al. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin Pharmacol Ther 2001;69:158-68.
24. Tanigawara Y et al. CYP2C19 genotype-related efficacy of omeprazole for the treatment of infection caused by Helicobacter pylori. Clin Pharmacol Ther 1999;66:528-34.
25. Aoyama N et al. Sufficient effect of 1-week omeprazole and amoxicillin dual treatment for Helicobacter pylori eradication in cytochrome P450 2C19 poor metabolizers. J Gastroenterol 1999;34 Suppl 11:80-3.
26. Inaba T et al. Helicobacter pylori infection: CYP2C19 genotype and serum ferritin. J Gastroenterol Hepatol 2002;17:748-53.
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28. SmPC's Losec en Prilosec (VS).

Date 05-03-2018

CYP2C19 UM: omeprazol **1841**

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

Recommendation:

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

Literature:

1. Park S et al. Effects of CYP2C19 genetic polymorphisms on PK/PD responses of omeprazole in Korean healthy volunteers. J Korean Med Sci 2017;32:729-736.
2. Chwiesko A et al. Effects of different omeprazole dosing on gastric pH in non-variceal upper gastrointestinal bleeding: a randomized prospective study. J Dig Dis 2016;17:588-599.
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36. SmPC's Losec en Prilosec (VS).

Date 05-03-2018

CYP2D6 IM: oxycodon **1587**

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:

1. Cajanus K et al. Analgesic plasma concentrations of oxycodone after surgery for breast cancer-which factors matter? Clin Pharmacol Ther 2017 Jun 23 [Epub ahead of print].
2. Stamer UM et al. CYP2D6 genotype dependent oxycodone metabolism in postoperative patients. PloS One 2013;8:e60239.
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Date 20-11-2017

CYP2D6 PM: oxycodon **1586**

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:

1. Cajanus K et al. Analgesic plasma concentrations of oxycodone after surgery for breast cancer-which factors matter? Clin Pharmacol Ther 2017 Jun 23 [Epub ahead of print].
2. Lam J et al. Putative association of ABCB1 2677G>T/A with oxycodone-induced central nervous system depression in breastfeeding mothers. Ther Drug Monit 2013;35:466-72.
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Date 20-11-2017

CYP2D6 UM: oxycodon **1588**

NO action is required for this gene-drug interaction.

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

Literature:

1. Cajanus K et al. Analgesic plasma concentrations of oxycodone after surgery for breast cancer-which factors matter? Clin Pharmacol Ther 2017 Jun 23 [Epub ahead of print].
2. Lam J et al. Putative association of ABCB1 2677G>T/A with oxycodone-induced central nervous system depression in breastfeeding mothers. Ther Drug Monit 2013;35:466-72.
3. Stamer UM et al. CYP2D6 genotype dependent oxycodone metabolism in postoperative patients. PloS One 2013;8:e60239.
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Date 20-11-2017

CYP2C19 IM: pantoprazol **1847**

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:

1. Deshpande N et al. Rapid and ultra-rapid metabolizers with CYP2C19*17 polymorphism do not respond to standard therapy with proton pump inhibitors. Meta Gene 2016;9:159-64.
2. Ormeci A et al. Effect of cytochrome P450 2C19 polymorphisms on the Helicobacter pylori eradication rate following two-week triple therapy with pantoprazole or rabeprazole. Eur Rev Med Pharmacol Sci 2016;20:879-85.
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17. Gawronska-Szklarz B et al. Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders with Helicobacter pylori infection. Eur J Clin Pharmacol 2005;61:375-9.
18. Kearns GL et al. Single-dose pharmacokinetics of oral and intravenous pantoprazole in children and adolescents. J Clin Pharmacol 2008;48:1356-65.

Date 05-03-2018

CYP2C19 PM: pantoprazol **1848**

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:

1. Deshpande N et al. Rapid and ultra-rapid metabolizers with CYP2C19*17 polymorphism do not respond to standard therapy with proton pump inhibitors. Meta Gene 2016;9:159-64.
2. Ormeci A et al. Effect of cytochrome P450 2C19 polymorphisms on the Helicobacter pylori eradication rate following two-week triple therapy with pantoprazole or rabeprazole. Eur Rev Med Pharmacol Sci 2016;20:879-85.
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9. Tseng PH et al. A comparative study of proton-pump inhibitor tests for Chinese reflux patients in relation to the CYP2C19 genotypes. J Clin Gastroenterol 2009;43:920-5.
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11. Choi KD et al. Optimal dose of intravenous pantoprazole in patients with peptic ulcer bleeding requiring endoscopic hemostasis in Korea. J Gastroenterol Hepatol 2009;24:1617-24.
12. Oh JH et al. Low-dose intravenous pantoprazole for optimal inhibition of gastric acid in Korean patients. J Gastroenterol Hepatol 2007;22:1429-34.
13. Oh JH et al. Effects of CYP2C19 and MDR1 genotype on the eradication rate of Helicobacter pylori infection by triple therapy with pantoprazole, amoxycillin and clarithromycin. J Gastroenterol Hepatol 2009;24:294-8.
14. Kang JM et al. Effect of the CYP2C19 polymorphism on the eradication rate of Helicobacter pylori infection by 7-day triple therapy with regular proton pump inhibitor dosage. J Gastroenterol Hepatol 2008;23:1287-91.
15. Kurzawski M et al. Effect of CYP2C19*17 gene variant on Helicobacter pylori eradication in peptic ulcer patients. Eur J Clin Pharmacol 2006;62:877-80.
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17. SPC's Pantozol en Protonix I.V. (VS).

Date 05-03-2018

CYP2C19 UM: pantoprazol **1849**

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:

1. Deshpande N et al. Rapid and ultra-rapid metabolizers with CYP2C19*17 polymorphism do not respond to standard therapy with proton pump inhibitors. Meta Gene 2016;9:159-64.
2. Ormeci A et al. Effect of cytochrome P450 2C19 polymorphisms on the Helicobacter pylori eradication rate following two-week triple therapy with pantoprazole or rabeprazole. Eur Rev Med Pharmacol Sci 2016;20:879-85.
3. Hsu PI et al. A randomized controlled study comparing reverse hybrid therapy and standard triple therapy for Helicobacter pylori infection. Medicine (Baltimore) 2015;94:e2104.
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5. Gawrońska-Szklarz B et al. CYP2C19 polymorphism affects single-dose pharmacokinetics of oral pantoprazole in healthy volunteers. Eur J Clin Pharmacol 2012;68:1267-74.
6. Sheu BS et al. CYP2C19 genotypes determine the efficacy of on-demand therapy of pantoprazole for reflux esophagitis as Los-Angeles grades C and D. J Gastroenterol Hepatol 2012;27:104-9.
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10. Hunfeld NG et al. A comparison of the acid-inhibitory effects of esomeprazole and pantoprazole in relation to pharmacokinetics and CYP2C19 polymorphism. Aliment Pharmacol Ther 2010;31:150-9.
11. Tseng PH et al. A comparative study of proton-pump inhibitor tests for Chinese reflux patients in relation to the CYP2C19 genotypes. J Clin Gastroenterol 2009;43:920-5.
12. Hunfeld NG et al. Effect of CYP2C19*2 and* 17 mutations on pharmacodynamics and kinetics of proton pump inhibitors in Caucasians. Br J Clin Pharmacol 2008;65:752-60.
13. Choi KD et al. Optimal dose of intravenous pantoprazole in patients with peptic ulcer bleeding requiring endoscopic hemostasis in Korea. J Gastroenterol Hepatol 2009;24:1617-24.
14. Oh JH et al. Low-dose intravenous pantoprazole for optimal inhibition of gastric acid in Korean patients. J Gastroenterol Hepatol 2007;22:1429-34.
15. Oh JH et al. Effects of CYP2C19 and MDR1 genotype on the eradication rate of Helicobacter pylori infection by triple therapy with pantoprazole, amoxycillin and clarithromycin. J Gastroenterol Hepatol 2009;24:294-8.
16. Kang JM et al. Effect of the CYP2C19 polymorphism on the eradication rate of Helicobacter pylori infection by 7-day triple therapy with regular proton pump inhibitor dosage. J Gastroenterol Hepatol 2008;23:1287-91.
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20. SPC's Pantozol en Protonix I.V. (VS).

Date 05-03-2018

CYP2D6 IM: paroxetine **1563**

NO action is needed for this gene-drug interaction.

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

Literature:

1. Janssen PK et al. Nonresponders to daily paroxetine and another SSRI in men with lifelong premature ejaculation: a pharmacokinetic dose-escalation study for a rare phenomenon. Korean J Urol 2014;55:599-607.
2. Saruwatari J et al. Possible impact of the CYP2D6*10 polymorphism on the nonlinear pharmacokinetic parameter estimates of paroxetine in Japanese patients with major depressive disorders. Pharmgenomics Pers Med 2014;7:121-7.
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4. Murata Y et al. Effects of the serotonin 1A, 2A, 2C, 3A, and 3B and serotonin transporter gene polymorphisms on the occurrence of paroxetine discontinuation syndrome. J Clin Psychopharmacol 2010;30:11-7.
5. Ververs FF et al. Effect of cytochrome P450 2D6 genotype on maternal paroxetine plasma concentrations during pregnancy. Clin Pharmacokinet 2009;48:677-83.
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14. Murphy G ea. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003;160:1830-5.
15. Ozdemir V ea. Paroxetine steady-state plasma concentration in relation to CYP2D6 genotype in extensive metabolizers. J Clin Psychopharmacol 1999;19:472-5.

Date 14-05-2018

CYP2D6 PM: paroxetine **1564**

NO action is needed for this gene-drug interaction.

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

Literature:

1. Ververs FF et al. Effect of cytochrome P450 2D6 genotype on maternal paroxetine plasma concentrations during pregnancy. Clin Pharmacokinet 2009;48:677-83.
2. Van Nieuwerburgh FC et al. Response to serotonin reuptake inhibitors in OCD is not influenced by common CYP2D6 polymorphisms. Int J Psychiatry Clin Pract 2009;13:345-348.
3. Gex-Fabry M et al. CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response. Ther Drug Monit 2008;30:474-82.
4. Kuhn UD et al. Reboxetine and cytochrome P450--comparison with paroxetine treatment in humans. Int J Clin Pharmacol Ther 2007;45:36-46.
5. Findling RL et al. Multiple dose pharmacokinetics of paroxetine in children and adolescents with major depressive disorder or obsessive-compulsive disorder. Neuropsychopharmacology 2006;31:1274-85.
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7. Sawamura K et al. Effects of dosage and CYP2D6-mutated allele on plasma concentration of paroxetine. Eur J Clin Pharmacol 2004;60:553-7.
8. Charlier C et al. Polymorphisms in the CYP 2D6 gene: association with plasma concentrations of fluoxetine and paroxetine. Ther Drug Monit 2003;25:738-42.
9. Murphy G et al. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003;160:1830-5.
10. Sindrup SH et al. Pharmacokinetics of the selective serotonin reuptake inhibitor paroxetine: nonlinearity and relation to the sparteine oxidation polymorphism. Clin Pharmacol Ther 1992;51:288-95.
11. Sindrup SH et al. The relationship between paroxetine and the sparteine oxidation polymorphism. Clin Pharmacol Ther 1992;51:278-87.

Date 14-05-2018

CYP2D6 UM: paroxetine **1565**

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

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

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

Literature:

1. Gex-Fabry M et al. CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response. Ther Drug Monit 2008;30:474-82.
2. Findling RL et al. Multiple dose pharmacokinetics of paroxetine in children and adolescents with major depressive disorder or obsessive-compulsive disorder. Neuropsychopharmacology 2006;31:1274-85.
3. Feng Y et al. Paroxetine: population pharmacokinetic analysis in late-life depression using sparse concentration sampling. Br J Clin Pharmacol 2006;61:558-69.
4. Güzey C et al. Low serum concentrations of paroxetine in CYP2D6 ultrarapid metabolizers. J Clin Psychopharmacol 2006;26:211-2.
5. Charlier C et al. Polymorphisms in the CYP 2D6 gene: association with plasma concentrations of fluoxetine and paroxetine. Ther Drug Monit 2003;25:738-42.
6. Murphy G et al. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003;160:1830-5.

Date 14-05-2018

CYP2D6 IM: pimozide **2448**

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 risk of an excessively high plasma concentration can be negated by following the dose recommendations provided below.

Recommendation:

- use no more than the following doses (80% of the standard maximum dose):
  - adults 16 mg/day
  - children 0.08 mg/kg per day to a maximum of 3 mg/day

Literature:

1. 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 en persoonlijke communicatie (gemiddelde dosisgecorrigeerde pimozidedalconcentraties).
2. Nucci G et al. Population pharmacokinetic modelling of pimozide and its relation to CYP2D6 genotype. Poster presented at the annual meeting of population approach group in Europe 2007.

Date 19-11-2018

CYP2D6 PM: pimozide **2447**

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 risk of an excessively high plasma concentration can be negated by following the dose recommendations provided below.

- use no more than the following doses (50% of the standard maximum dose):
  - adults 10 mg/day
  - children 0.05 mg/kg per day to a maximum of 2 mg/day

Literature:

1. 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 en persoonlijke communicatie (gemiddelde dosisgecorrigeerde pimozidedalconcentraties).
2. Nucci G et al. Population pharmacokinetic modelling of pimozide and its relation to CYP2D6 genotype. Poster presented at the annual meeting of population approach group in Europe 2007.
3. Desta Z et al. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). Clin Pharmacol Ther 1999;65:10-20.
4. Pharmacogenetic changes to the FDA-approved Orap (pimozide) label include adult and pediatric dosing recommendations for CYP2D6 poor metabolizers. FDA-nieuwsbericht 27-09-11.
5. SPC Orap (NL en VS).

Date 19-11-2018

CYP2D6 UM: pimozide **2449**

NO action is required for this gene-drug interaction.

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

Literature:

1. 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 en persoonlijke communicatie (gemiddelde dosisgecorrigeerde pimozidedalconcentraties).

Date 19-11-2018

CYP2C19 IM: prasugrel **2546**

This is NOT a gene-drug interaction.

Literature:

1. Lee CR et al. Clinical outcomes and sustainability of using CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. Circ Genom Precis Med 2018;11:e002069.
2. Ogawa H et al. Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. J Cardiol 2016;68:29-36.
3. Doll JA et al. Impact of CYP2C19 metabolizer status on patients with ACS treated with prasugrel versus clopidogrel. J Am Coll Cardiol 2016;67:936-47.
4. Varenhorst C et al. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J 2009;30:1744-52.
5. Mega JL et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553-60.
6. Brandt JT et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007;5:2429-36.
7. SPC Efient (NL en VS).

Date 19-11-2018

CYP2C19 PM: prasugrel **2545**

This is NOT a gene-drug interaction.

Literature:

1. Lee CR et al. Clinical outcomes and sustainability of using CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. Circ Genom Precis Med 2018;11:e002069.
2. Deiman BA et al. Reduced number of cardiovascular events and increased cost-effectiveness by genotype-guided antiplatelet therapy in patients undergoing percutaneous coronary interventions in the Netherlands. Neth Heart J 2016;24:589-99.
3. Ogawa H et al. Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. J Cardiol 2016;68:29-36.
4. Doll JA et al. Impact of CYP2C19 metabolizer status on patients with ACS treated with prasugrel versus clopidogrel. J Am Coll Cardiol 2016;67:936-47.
5. Varenhorst C et al. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J 2009;30:1744-52.
6. Mega JL et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553-60.
7. Brandt JT et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007;5:2429-36.
8. SPC Efient (NL en VS).

Date 19-11-2018

CYP2C19 UM: prasugrel **2547**

This is NOT a gene-drug interaction.

Literature:

1. Mega JL et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553-60.
2. SPC Efient (NL en VS).

Date 19-11-2018

CYP2D6 IM: propafenon **1596**

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

Recommendation:

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

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

Literature:

1. Mörike K et al. Propafenone for the prevention of atrial tachyarrhythmias after cardiac surgery: a randomized, double-blind placebo-controlled trial. Clin Pharmacol Ther 2008;84:104-10.
2. Chen B et al. Influence of CYP2D6*10B genotype on pharmacokinetics of propafenone enantiomers in Chinese subjects. Acta Pharmacol Sin 2003;24:1277-80.
3. Cai WM et al. Effect of CYP2D6*10 genotype on propafenone pharmacodynamics in Chinese patients with ventricular arrhythmia. Acta Pharmacol Sin 2002;23:1040-4.
4. Cai WM et al. Simultaneous modeling of pharmacokinetics and pharmacodynamics of propafenone in healthy subjects. Acta Pharmacol Sin 2001;22:956-60.

Date 24-08-2016

CYP2D6 PM: propafenon **1595**

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

Recommendation:

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

Literature:

1. Mörike K et al. Propafenone for the prevention of atrial tachyarrhythmias after cardiac surgery: a randomized, double-blind placebo-controlled trial. Clin Pharmacol Ther 2008;84:104-10.
2. Jazwinska-Tarnawska E et al. The influence of CYP2D6 polymorphism on the antiarrhythmic efficacy of propafenone in patients with paroxysmal atrial fibrillation during 3 months propafenone prophylactic treatment. Int J Clin Pharmacol Ther 2001;39:288-92.
3. Chow MS et al. Evaluation of CYP2D6 oxidation of dextromethorphan and propafenone in a Chinese population with atrial fibrillation. J Clin Pharmacol 2001;41:92-6.
4. Labbe L et al. Pharmacokinetic and pharmacodynamic interaction between mexiletine and propafenone in human beings. Clin Pharmacol Ther 2000;68:44-57.
5. Dilger K et al. Consequences of rifampicin treatment on propafenone disposition in extensive and poor metabolizers of CYP2D6. Pharmacogenetics 1999;9:551-9.
6. Cai WM et al. The influence of CYP2D6 activity on the kinetics of propafenone enantiomers in Chinese subjects. Br J Clin Pharmacol 1999;47:553-6.
7. Morike K et al. Propafenone in a usual dose produces severe side-effects: the impact of genetically determined metabolic status on drug therapy. J Intern Med 1995;238:469-72.
8. Morike KE et al. Quinidine-enhanced beta-blockade during treatment with propafenone in extensive metabolizer human subjects. Clin Pharmacol Ther 1994;55:28-34.
9. Lee JT et al. The role of genetically determined polymorphic drug metabolism in the beta-blockade produced by propafenone. N Engl J Med 1990;21:1764-8.
10. Siddoway LA et al. Polymorphism of propafenone metabolism and disposition in man: clinical and pharmacokinetic consequences. Circulation 1987;75:785-91.
11. SPC Rytmonorm.
12. SPC Rythmol SR (VS).

Date 24-08-2016

CYP2D6 UM: propafenon **1597**

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

Recommendation:

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

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

Literature:

1. Mörike K et al. Propafenone for the prevention of atrial tachyarrhythmias after cardiac surgery: a randomized, double-blind placebo-controlled trial. Clin Pharmacol Ther 2008;84:104-10.
2. Jazwinska-Tarnawska E et al. The influence of CYP2D6 polymorphism on the antiarrhythmic efficacy of propafenone in patients with paroxysmal atrial fibrillation during 3 months propafenone prophylactic treatment. Int J Clin Pharmacol Ther 2001;39:288-92.

Date 24-08-2016

CYP2D6 IM: quetiapine **2394**

This is NOT a gene-drug interaction.

Literature:

1. Xu Q et al. Association studies of genomic variants with treatment response to risperidone, clozapine, quetiapine and chlorpromazine in the Chinese Han population. Pharmacogenomics J 2016;16:357-65.
2. Bakken GV et al. Impact of genetic variability in CYP2D6, CYP3A5, and ABCB1 on serum concentrations of quetiapine and N-desalkylquetiapine in psychiatric patients. Ther Drug Monit 2015;37:256-61.
3. Kato D et al. Delirium resolving upon switching from risperidone to quetiapine: implication of CYP2D6 genotype. Psychosomatics 2005;46:374-5.

Date 14-09-2020

CYP2D6 PM: quetiapine **2393**

This is NOT a gene-drug interaction.

Literature:

1. Xu Q et al. Association studies of genomic variants with treatment response to risperidone, clozapine, quetiapine and chlorpromazine in the Chinese Han population. Pharmacogenomics J 2016;16:357-65.
2. Bakken GV et al. Impact of genetic variability in CYP2D6, CYP3A5, and ABCB1 on serum concentrations of quetiapine and N-desalkylquetiapine in psychiatric patients. Ther Drug Monit 2015;37:256-61.

Date 14-09-2020

CYP2D6 UM: quetiapine **2395**

This is NOT a gene-drug interaction.

Literature:

1. Bakken GV et al. Impact of genetic variability in CYP2D6, CYP3A5, and ABCB1 on serum concentrations of quetiapine and N-desalkylquetiapine in psychiatric patients. Ther Drug Monit 2015;37:256-61.
2. Khazaal Y et al. Use of high doses of quetiapine in bipolar disorder episodes are not linked to high activity of cytochrome P450 3A4 and/or cytochrome P4502D6. Psychiatr Q 2013;84:329-35.

Date 14-09-2020

CYP2C19 IM: rabeprazol **1856**

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:

1. Nakamura K et al. Limited effect of rebamipide in addition to proton pump inhibitor (PPI) in the treatment of post-endoscopic submucosal dissection gastric ulcers: a randomized controlled trial comparing PPI plus rebamipide combination therapy with PPI monotherapy. Gut Liver 2016;10:917-924.
2. Tang HL et al. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. PLoS One 2013;8:e62162.
3. Kinoshita Y et al. Randomised clinical trial: a multicentre, double-blind, placebo- controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. Aliment Pharmacol Ther 2011;33:213-24.
4. Lay CS et al. Correlation of CYP2C19 genetic polymorphisms with Helicobacter pylori eradication in patients with cirrhosis and peptic ulcer. J Chin Med Assoc 2010;73:188-93.
5. Saitoh T et al. Influences of CYP2C19 polymorphism on recurrence of reflux esophagitis during proton pump inhibitor maintenance therapy. Hepatogastroenterology 2009;56:703-6.
6. Yamano HO et al. Plasma concentration of rabeprazole after 8-week administration in gastroesophageal reflux disease patients and intragastric pH elevation. J Gastroenterol Hepatol 2008;23:534-40.
7. Lee YC et al. Influence of cytochrome P450 2C19 genetic polymorphism and dosage of rabeprazole on accuracy of proton-pump inhibitor testing in Chinese patients with gastroesophageal reflux disease. J Gastroenterol Hepatol 2007;22:1286-92.
8. Li ZS et al. Effect of esomeprazole and rabeprazole on intragastric pH in healthy Chinese: an open, randomized crossover trial. J Gastroenterol Hepatol 2007;22:815-20.
9. Ariizumi K et al. Therapeutic effects of 10 mg/day rabeprazole administration on reflux esophagitis was not influenced by the CYP2C19 polymorphism. J Gastroenterol Hepatol 2006;21:1428-34.
10. Hu YM et al. Pharmacodynamic and kinetic effect of rabeprazole on serum gastrin level in relation to CYP2C19 polymorphism in Chinese Hans. World J Gastroenterol 2006;12:4750-3.
11. Sugimoto M et al. Comparison of an increased dosage regimen of rabeprazole versus a concomitant dosage regimen of famotidine with rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotypes. Clin Pharmacol Ther 2005;77:302-11.
12. Sugimoto M et al. Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status. Clin Pharmacol Ther 2004;76:290-301.
13. Shimatani 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.
14. Shirai N et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. Aliment Pharmacol Ther 2001;15:1929-37.
15. Horai Y et al. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. Aliment Pharmacol Ther 2001;15:793-803.
16. Adachi K et al. CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. Aliment Pharmacol Ther 2000;14:1259-66.
17. Ando T et al. Endoscopic analysis of gastric ulcer after one week's treatment with omeprazole and rabeprazole in relation to CYP2C19 genotype. Dig Dis Sci 2008;53:933-7.
18. Ando T et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. Dig Dis Sci 2005;50:1625-31.
19. Yang JC et al. Pharmacokinetic- pharmacodynamic analysis of the role of CYP2C19 genotypes in short-term rabeprazole-based triple therapy against Helicobacter pylori. Br J Clin Pharmacol 2009;67:503-10.
20. Zhao F et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter 2008;13:532-41.
21. Kuwayama H et al. Rabeprazole-based eradication therapy for Helicobacter pylori: a large-scale study in Japan. Aliment Pharmacol Ther 2007;25:1105-13.

22. Miki I et al. Impact of clarithromycin resistance and CYP2C19 genetic polymorphism on treatment efficacy of Helicobacter pylori infection with lansoprazole- or rabeprazole-based triple therapy in Japan. Eur J Gastroenterol Hepatol 2003;15:27-33.
23. Dojo M et al. Effects of CYP2C19 gene polymorphism on cure rates for Helicobacter pylori infection by triple therapy with proton pump inhibitor (omeprazole or rabeprazole), amoxycillin and clarithromycin in Japan. Dig Liver Dis 2001;33:671-5.
24. Inaba T et al. Helicobacter pylori infection: CYP2C19 genotype and serum ferritin. J Gastroenterol Hepatol 2002;17:748-53.
25. SPC Pariet.

Date 05-03-2018

CYP2C19 PM: rabeprazol **1857**

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:

1. Nakamura K et al. Limited effect of rebamipide in addition to proton pump inhibitor (PPI) in the treatment of post-endoscopic submucosal dissection gastric ulcers: a randomized controlled trial comparing PPI plus rebamipide combination therapy with PPI monotherapy. Gut Liver 2016;10:917-924.
2. Tang HL et al. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. PLoS One 2013;8:e62162.
3. Kinoshita Y et al. Randomised clinical trial: a multicentre, double-blind, placebo- controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. Aliment Pharmacol Ther 2011;33:213-24.
4. Lay CS et al. Correlation of CYP2C19 genetic polymorphisms with Helicobacter pylori eradication in patients with cirrhosis and peptic ulcer. J Chin Med Assoc 2010;73:188-93.
5. Tseng PH et al. A comparative study of proton-pump inhibitor tests for Chinese reflux patients in relation to the CYP2C19 genotypes. J Clin Gastroenterol 2009;43:920-5.
6. Saitoh T et al. Influences of CYP2C19 polymorphism on recurrence of reflux esophagitis during proton pump inhibitor maintenance therapy. Hepatogastroenterology 2009;56:703-6.
7. Yamano HO et al. Plasma concentration of rabeprazole after 8-week administration in gastroesophageal reflux disease patients and intragastric pH elevation. J Gastroenterol Hepatol 2008;23:534-40.
8. Lee YC et al. Influence of cytochrome P450 2C19 genetic polymorphism and dosage of rabeprazole on accuracy of proton-pump inhibitor testing in Chinese patients with gastroesophageal reflux disease. J Gastroenterol Hepatol 2007;22:1286-92.
9. Li ZS et al. Effect of esomeprazole and rabeprazole on intragastric pH in healthy Chinese: an open, randomized crossover trial. J Gastroenterol Hepatol 2007;22:815-20.
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.
11. Hu YM et al. Pharmacodynamic and kinetic effect of rabeprazole on serum gastrin level in relation to CYP2C19 polymorphism in Chinese Hans. World J Gastroenterol 2006;12:4750-3.
12. Sugimoto M et al. Comparison of an increased dosage regimen of rabeprazole versus a concomitant dosage regimen of famotidine with rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotypes. Clin Pharmacol Ther 2005;77:302-11.
13. Sugimoto M et al. Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status. Clin Pharmacol Ther 2004;76:290-301.
14. Shimatani 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.
15. Shirai N et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. Aliment Pharmacol Ther 2001;15:1929-37.
16. Horai Y et al. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. Aliment Pharmacol Ther 2001;15:793-803.
17. Adachi K et al. CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. Aliment Pharmacol Ther 2000;14:1259-66.
18. Ando T et al. Endoscopic analysis of gastric ulcer after one week's treatment with omeprazole and rabeprazole in relation to CYP2C19 genotype. Dig Dis Sci 2008;53:933-7.
19. Ji S et al. Comparison of the efficacy of rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of peptic ulcer diseases. J Gastroenterol Hepatol 2006;21: 1381-7.
20. Ando T et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. Dig Dis Sci 2005;50:1625-31.
21. Yang JC et al. Pharmacokinetic- pharmacodynamic analysis of the role of CYP2C19 genotypes in short-term rabeprazole-based triple therapy against Helicobacter pylori. Br J Clin Pharmacol 2009;67:503-10.
22. Zhao F et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter 2008;13:532-41.
23. Kuwayama H et al. Rabeprazole-based eradication therapy for Helicobacter pylori: a large-scale study in Japan. Aliment Pharmacol Ther 2007;25:1105-13.
24. Miki I et al. Impact of clarithromycin resistance and CYP2C19 genetic polymorphism on treatment efficacy of Helicobacter pylori infection with lansoprazole- or rabeprazole-based triple therapy in Japan. Eur J Gastroenterol Hepatol 2003;15:27-33.
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26. Hokari K et al. Efficacy of triple therapy with rabeprazole for Helicobacter pylori infection and CYP2C19 genetic polymorphism. Aliment Pharmacol Ther 2001;15:1479-84.
27. Inaba T et al. Helicobacter pylori infection: CYP2C19 genotype and serum ferritin. J Gastroenterol Hepatol 2002;17:748-53.
28. SPC's Pariet en Aciphex (VS).

Date 05-03-2018

CYP2C19 UM: rabeprazol **1858**

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:

1. Nakamura K et al. Limited effect of rebamipide in addition to proton pump inhibitor (PPI) in the treatment of post-endoscopic submucosal dissection gastric ulcers: a randomized controlled trial comparing PPI plus rebamipide combination therapy with PPI monotherapy. Gut Liver 2016;10:917-924.
2. Tang HL et al. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. PLoS One 2013;8:e62162.
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5. Tseng PH et al. A comparative study of proton-pump inhibitor tests for Chinese reflux patients in relation to the CYP2C19 genotypes. J Clin Gastroenterol 2009;43:920-5.
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7. Yamano HO et al. Plasma concentration of rabeprazole after 8-week administration in gastroesophageal reflux disease patients and intragastric pH elevation. J Gastroenterol Hepatol 2008;23:534-40.
8. Lee YC et al. Influence of cytochrome P450 2C19 genetic polymorphism and dosage of rabeprazole on accuracy of proton-pump inhibitor testing in Chinese patients with gastroesophageal reflux disease. J Gastroenterol Hepatol 2007;22:1286-92.
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11. Hu YM et al. Pharmacodynamic and kinetic effect of rabeprazole on serum gastrin level in relation to CYP2C19 polymorphism in Chinese Hans. World J Gastroenterol 2006;12:4750-3.
12. Sugimoto M et al. Comparison of an increased dosage regimen of rabeprazole versus a concomitant dosage regimen of famotidine with rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotypes. Clin Pharmacol Ther 2005;77:302-11.
13. Sugimoto M et al. Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status. Clin Pharmacol Ther 2004;76:290-301.
14. Shimatani 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.
15. Shirai N et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. Aliment Pharmacol Ther 2001;15:1929-37.
16. Horai Y et al. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. Aliment Pharmacol Ther 2001;15:793-803.
17. Adachi K et al. CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. Aliment Pharmacol Ther 2000;14:1259-66.
18. Ando T et al. Endoscopic analysis of gastric ulcer after one week's treatment with omeprazole and rabeprazole in relation to CYP2C19 genotype. Dig Dis Sci 2008;53:933-7.
19. Ji S et al. Comparison of the efficacy of rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of peptic ulcer diseases. J Gastroenterol Hepatol 2006;21: 1381-7.
20. Ando T et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. Dig Dis Sci 2005;50:1625-31.
21. Yang JC et al. Pharmacokinetic- pharmacodynamic analysis of the role of CYP2C19 genotypes in short-term rabeprazole-based triple therapy against Helicobacter pylori. Br J Clin Pharmacol 2009;67:503-10.
22. Zhao F et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter 2008;13:532-41.
23. Kuwayama H et al. Rabeprazole-based eradication therapy for Helicobacter pylori: a large-scale study in Japan. Aliment Pharmacol Ther 2007;25:1105-13.
24. Miki I et al. Impact of clarithromycin resistance and CYP2C19 genetic polymorphism on treatment efficacy of Helicobacter pylori infection with lansoprazole- or rabeprazole-based triple therapy in Japan. Eur J Gastroenterol Hepatol 2003;15:27-33.
25. Dojo M et al. Effects of CYP2C19 gene polymorphism on cure rates for Helicobacter pylori infection by triple therapy with proton pump inhibitor (omeprazole or rabeprazole), amoxycillin and clarithromycin in Japan. Dig Liver Dis 2001;33:671-5.
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27. Inaba T et al. Helicobacter pylori infection: CYP2C19 genotype and serum ferritin. J Gastroenterol Hepatol 2002;17:748-53.
28. SPC's Pariet en Aciphex (VS).

Date 05-03-2018

CYP2D6 IM: risperidon **1536**

NO action is needed for this gene-drug interaction.

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

Literature:

1. Jukic MM et al. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry 2019;6:418-26.
2. Oshikoya KA et al. CYP2D6 genotype and adverse events to risperidone in children and adolescents. Pediatr Res 2019;85:602-6.
3. Schoretsanitis G et al. Prolactin levels: sex differences in the effects of risperidone, 9-hydroxyrisperidone levels, CYP2D6 and ABCB1 variants. Pharmacogenomics 2018;19:815-823.
4. Kaur G et al. Identification of genetic correlates of response to risperidone: findings of a multicentric schizophrenia study from India. Asian J Psychiatr 2017;29:174-82.
5. Ivaturi V et al. Exposure-response analysis after subcutaneous administration of RBP-7000, a once-a-month long-acting Atrigel formulation of risperidone. Br J Clin Pharmacol 2017;83:1476-98.
6. Xu Q et al. Association studies of genomic variants with treatment response to risperidone, clozapine, quetiapine and chlorpromazine in the Chinese Han population. Pharmacogenomics J 2016;16:357-65.
7. Sukasem C et al. Impact of pharmacogenetic markers of CYP2D6 and DRD2 on prolactin response in risperidone-treated Thai children and adolescents with autism spectrum disorders. J Clin Psychopharmacol 2016;36:141-6.
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9. dos Santos Júnior A et al. Hyperprolactinemia in children and adolescents with use of risperidone: clinical and molecular genetics aspects. J Child Adolesc Psychopharmacol 2015;25:738-48.
10. Vandenberghe F et al. Genetics-based population pharmacokinetics and pharmacodynamics of risperidone in a psychiatric cohort. Clin Pharmacokinet 2015;54:1259-72.
11. 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.
12. Suzuki Y et al. Effect of risperidone metabolism and P-glycoprotein gene polymorphism on QT interval in patients with schizophrenia. Pharmacogenomics J 2014;14:452-6.
13. Almoguera B et al. CYP2D6 poor metabolizer status might be associated with better response to risperidone treatment. Pharmacogenet Genomics 2013 ;23:627-30.
14. Almoguera B et al. Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population. Pharmacogenomics J 2013; 13:197-204. PubMed PMID: 22212732.
15. Mas S et al. Intuitive pharmacogenetics: spontaneous risperidone dosage is related to CYP2D6, CYP3A5 and ABCB1 genotypes. Pharmacogenomics J 2012; 12:255-9.
16. Jovanović N et al. The role of CYP2D6 and ABCB1 pharmacogenetics in drug-naïve patients with first-episode schizophrenia treated with risperidone. Eur J Clin Pharmacol 2010; 66:1109-17.
17. Novalbos J et al. Effects of CYP2D6 genotype on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. J Clin Psychopharmacol 2010;30:504-11.
18. Wang L et al. Serum prolactin levels, plasma risperidone levels, polymorphism of cytochrome P450 2D6 and clinical response in patients with schizophrenia. J Psychopharmacol 2007;21:837-42.
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. Pharmacopsychiatry 2007;40:93-102.
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30. Bork JA et al. A pilot study on risperidone metabolism: the role of cytochromes P450 2D6 and 3A. J Clin Psychiatry 1999;60:469-76.

Date 17-09-2019

CYP2D6 PM: risperidon **1537**

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. Jukic MM et al. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry 2019;6:418-26.
2. Oshikoya KA et al. CYP2D6 genotype and adverse events to risperidone in children and adolescents. Pediatr Res 2019;85:602-6.
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4. Kaur G et al. Identification of genetic correlates of response to risperidone: findings of a multicentric schizophrenia study from India. Asian J Psychiatr 2017;29:174-82.
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12. Gassó P et al. Effect of CYP2D6 on risperidone pharmacokinetics and extrapyramidal symptoms in healthy volunteers: results from a pharmacogenetic clinical trial. Pharmacogenomics 2014;15:17-28.
13. Almoguera B et al. CYP2D6 poor metabolizer status might be associated with better response to risperidone treatment. Pharmacogenet Genomics 2013 ;23:627-30.
14. Almoguera B et al. Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population. Pharmacogenomics J 2013; 13:197-204. PubMed PMID: 22212732.
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16. Novalbos J et al. Effects of CYP2D6 genotype on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. J Clin Psychopharmacol 2010;30:504-11.
17. Jovanović N et al. The role of CYP2D6 and ABCB1 pharmacogenetics in drug-naïve patients with first-episode schizophrenia treated with risperidone. Eur J Clin Pharmacol 2010; 66:1109-17.
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24. Bork JA et al. A pilot study on risperidone metabolism: the role of cytochromes P450 2D6 and 3A. J Clin Psychiatry 1999;60:469-76.
25. SPC Risperdal (NL en VS).

Date 17-09-2019

CYP2D6 UM: risperidon **1535**

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:

1. Jukic MM et al. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry 2019;6:418-26.
2. Oshikoya KA et al. CYP2D6 genotype and adverse events to risperidone in children and adolescents. Pediatr Res 2019;85:602-6.
3. Schoretsanitis G et al. Prolactin levels: sex differences in the effects of risperidone, 9-hydroxyrisperidone levels, CYP2D6 and ABCB1 variants. Pharmacogenomics 2018;19:815-823.
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6. Almoguera B et al. CYP2D6 poor metabolizer status might be associated with better response to risperidone treatment. Pharmacogenet Genomics 2013 ;23:627-30.
7. Almoguera B et al. Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population. Pharmacogenomics J 2013; 13:197-204. PubMed PMID: 22212732.
8. Mas S et al. Intuitive pharmacogenetics: spontaneous risperidone dosage is related to CYP2D6, CYP3A5 and ABCB1 genotypes. Pharmacogenomics J 2012; 12:255-9.
9. Novalbos J et al. Effects of CYP2D6 genotype on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. J Clin Psychopharmacol 2010;30:504-11.
10. 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. Pharmacopsychiatry 2007;40:93-102.
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13. Guzey C et al. Risperidone metabolism and the impact of being a cytochrome P450 2D6 ultrarapid metabolizer. J Clin Psychiatry 2000;61:600-1.
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Date 17-09-2019

CYP2C19 IM: sertraline **2008**

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:

1. Saiz-Rodríguez M et al. Effect of polymorphisms on the pharmacokinetics, pharmacodynamics and safety of sertraline in healthy volunteers. Basic Clin Pharmacol Toxicol 2018;122:501-511.
2. AlOlaby RR et al. Molecular biomarkers predictive of sertraline treatment response in young children with fragile X syndrome. Brain Dev 2017;39:483-492.
3. Yuce-Artun N et al. Influence of CYP2B6 and CYP2C19 polymorphisms on sertraline metabolism in major depression patients. Int J Clin Pharm 2016;38:388-94.
4. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.
5. Rudberg I et al. Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. Eur J Clin Pharmacol 2008;64:1181-8.
6. Wang JH et al. Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. Clin Pharmacol Ther 2001;70:42-7.

Date 14-05-2018

CYP2C19 PM: sertraline **2009**

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:

1. AlOlaby RR et al. Molecular biomarkers predictive of sertraline treatment response in young children with fragile X syndrome. Brain Dev 2017;39:483-492.
2. Yuce-Artun N et al. Influence of CYP2B6 and CYP2C19 polymorphisms on sertraline metabolism in major depression patients. Int J Clin Pharm 2016;38:388-94.
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4. Rudberg I et al. Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. Eur J Clin Pharmacol 2008;64:1181-8.
5. Grasmader K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.
6. Wang JH et al. Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. Clin Pharmacol Ther 2001;70:42-7.
7. SPC Zoloft.

Date 14-05-2018

CYP2C19 UM: sertraline **2010**

NO action is needed for this gene-drug interaction.

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

Literature:

1. AlOlaby RR et al. Molecular biomarkers predictive of sertraline treatment response in young children with fragile X syndrome. Brain Dev 2017;39:483-492.
2. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.
3. Rudberg I et al. Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. Eur J Clin Pharmacol 2008;64:1181-8.

Date 14-05-2018

CYP2D6 IM: sertraline **3513**

This is NOT a gene-drug interaction.

Literature:

1. Saiz-Rodríguez M et al. Effect of polymorphisms on the pharmacokinetics, pharmacodynamics and safety of sertraline in healthy volunteers. Basic Clin Pharmacol Toxicol 2018;122:501-511.

2. AlOlaby RR et al. Molecular biomarkers predictive of sertraline treatment response in young children with fragile X syndrome. Brain Dev 2017;39:483-492.
3. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.

Date 14-05-2018

CYP2D6 PM: sertraline **3512**

This is NOT a gene-drug interaction.

Literature:

1. Saiz-Rodríguez M et al. Effect of polymorphisms on the pharmacokinetics, pharmacodynamics and safety of sertraline in healthy volunteers. Basic Clin Pharmacol Toxicol 2018;122:501-511.
2. AlOlaby RR et al. Molecular biomarkers predictive of sertraline treatment response in young children with fragile X syndrome. Brain Dev 2017;39:483-492.
3. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.
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Date 14-05-2018

CYP2D6 UM: sertraline **3514**

This is NOT a gene-drug interaction.

Literature:

1. Saiz-Rodríguez M et al. Effect of polymorphisms on the pharmacokinetics, pharmacodynamics and safety of sertraline in healthy volunteers. Basic Clin Pharmacol Toxicol 2018;122:501-511.
2. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.

Date 14-05-2018

SLCO1B1 521CC: simvastatine **4056**

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

1. Choose an alternative
   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 CYP3A4 inhibitors.

Literature:

1. Xiang Q et al. Association between SLCO1B1 T521C polymorphism and risk of statin-induced myopathy: a meta-analysis. Pharmacogenomics J 2018;18:721-9.
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;24:240S-247S.
3. Kitzmiller JP et al. Candidate-gene study of functional polymorphisms in SLCO1B1 and CYP3A4/5 and the cholesterol-lowering response to simvastatin. Clin Transl Sci 2017;10:172-7.
4. Jiang J et al. Association between SLCO1B1 -521T>C and -388A>G polymorphisms and risk of statin-induced adverse drug reactions: a meta-analysis. Springerplus 2016;5:1368.
5. Hou Q et al. Association between SLCO1B1 gene T521C polymorphism and statin-related myopathy risk: a meta-analysis of case-control studies. Medicine (Baltimore) 2015;94:e1268.
6. Luzum JA et al. Individual and combined associations of genetic variants in CYP3A4, CYP3A5, and SLCO1B1 with simvastatin and simvastatin acid plasma concentrations. J Cardiovasc Pharmacol 2015;66:80-5.
7. Dou Y et al. Meta-analysis of the SLCO1B1 c.521T>C variant reveals slight influence on the lipid-lowering efficacy of statins. Ann Lab Med 2015;35:329-35.
8. de Keyser CE et al. The SLCO1B1 c.521T>C polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. Pharmacogenet Genomics 2014;24:43-51.
9. Carr DF et al. SLCO1B1 genetic variant associated with statin-induced myopathy: a proof-of-concept study using the Clinical Practice Research Datalink. Clin Pharmacol Ther 2013;94:695-701.
10. Hopewell JC et al. Impact of common genetic variation on response to simvastatin therapy among 18 705 participants in the Heart Protection Study. Eur Heart J 2013;34:982-92.
11. Hu M et al. Intronic variants in SLCO1B1 related to statin-induced myopathy are associated with the low-density lipoprotein cholesterol response to statins in Chinese patients with hyperlipidaemia. Pharmacogenet Genomics 2012;22:803-6.
12. Brunham LR et al. Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. Pharmacogenomics J 2012;12:233-7.
13. Sortica VA et al. SLCO1B1 gene variability influences lipid-lowering efficacy on simvastatin therapy in Southern Brazilians. Clin Chem Lab Med 2012;50:441-8.
14. Bailey KM et al. Hepatic metabolism and transporter gene variants enhance response to rosuvastatin in patients with acute myocardial infarction: the GEOSTAT-1 Study. Circ Cardiovasc Genet 2010;3:276-85.
15. Voora D et al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol 2009;54:1609-16.
16. Pasanen MK et al. Polymorphism of the hepatic influx transporter organic anion transporting polypeptide 1B1 is associated with increased cholesterol synthesis rate. Pharmacogenet Genomics 2008;18:921-6.
17. SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy -- a genomewide study. N Engl J Med 2008;359:789-99.
18. Pasanen MK et al. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics 2006;16:873-9.
19. Ramsey LB et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther 2014;96:423-8.
20. SmPC Zocor.

Date 18-05-2020

SLCO1B1 521TC: simvastatine **4055**

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 CYP3A4 inhibitors.
2. If an alternative is not an option:
   1. Avoid simvastatin doses exceeding 40 mg/day
   2. Advise the patient to contact their doctor in the event of muscle symptoms.

Literature:

1. Xiang Q et al. Association between SLCO1B1 T521C polymorphism and risk of statin-induced myopathy: a meta-analysis. Pharmacogenomics J 2018;18:721-9.
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;24:240S-247S.
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7. Dou Y et al. Meta-analysis of the SLCO1B1 c.521T>C variant reveals slight influence on the lipid-lowering efficacy of statins. Ann Lab Med 2015;35:329-35.
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10. Hopewell JC et al. Impact of common genetic variation on response to simvastatin therapy among 18 705 participants in the Heart Protection Study. Eur Heart J 2013;34:982-92.
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12. Brunham LR et al. Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. Pharmacogenomics J 2012;12:233-7.
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18. Pasanen MK et al. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics 2006;16:873-9.
19. Ramsey LB et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther 2014;96:423-8.
20. SmPC Zocor.

Date 18-05-2020

CYP2C9 *1/*2: siponimod **7160**

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. Gardin A et al. Siponimod pharmacokinetics, safety, and tolerability in combination with the potent CYP3A4 inhibitor itraconazole in healthy subjects with different CYP2C9 genotypes. Eur J Clin Pharmacol 2019;75:1565-74.
2. SmPC Mayzent (NL en VS).

Date 12-03-2020

CYP2C9 *1/*3: siponimod **7161**

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:

1. Gardin A et al. Siponimod pharmacokinetics, safety, and tolerability in combination with the potent CYP3A4 inhibitor itraconazole in healthy subjects with different CYP2C9 genotypes. Eur J Clin Pharmacol 2019;75:1565-74.
2. SmPC Mayzent (NL en VS).

Date 12-03-2020

CYP2C9 *2/*2: siponimod **7162**

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 **7163**

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:

1. Gardin A et al. Effect of fluconazole coadministration and CYP2C9 genetic polymorphism on siponimod pharmacokinetics in healthy subjects. Clin Pharmacokinet 2019;58:349-61.
2. SmPC Mayzent (NL en VS).

Date 12-03-2020

CYP2C9 *3/*3: siponimod **7164**

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:

1. Gardin A et al. Effect of fluconazole coadministration and CYP2C9 genetic polymorphism on siponimod pharmacokinetics in healthy subjects. Clin Pharmacokinet 2019;58:349-61.
2. SmPC Mayzent (NL en VS).

Date 12-03-2020

CYP2C9 IM: siponimod **7165**

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:

1. Gardin A et al. Siponimod pharmacokinetics, safety, and tolerability in combination with the potent CYP3A4 inhibitor itraconazole in healthy subjects with different CYP2C9 genotypes. Eur J Clin Pharmacol 2019;75:1565-74.
2. SmPC Mayzent (NL en VS).

Date 12-03-2020

CYP2C9 PM: siponimod **7166**

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:

1. Gardin A et al. Effect of fluconazole coadministration and CYP2C9 genetic polymorphism on siponimod pharmacokinetics in healthy subjects. Clin Pharmacokinet 2019;58:349-61.
2. SmPC Mayzent (NL en VS).

Date 12-03-2020

CYP2D6 IM: sotalol **2540**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2D6 PM: sotalol **2539**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP2D6 UM: sotalol **2541**

This is NOT a gene-drug interaction.

Literature:
-

Date 24-08-2016

CYP3A5 heterozygote expresser: tacrolimus **2358**

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

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

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

- LIVER transplantation:

In addition to the patient's genotype, the metabolism of tacrolimus is also determined by the genotype of the transplanted liver.
- LIVER is also of the genotype HETEROZYGOUS EXPRESSER:
- Use 1.5 times the normal initial dose
Adjustment of the dose should then be based on therapeutic drug monitoring.
- LIVER has a DIFFERENT genotype:
There is insufficient evidence in the literature to support a dose recommendation.

Literature:

1. Largeau B et al. Comparison of tacrolimus starting doses based on CYP3A5 phenotype or genotype in kidney transplant recipients. Prog Transplant 2019:1526924819873905 [Epub ahead of print].
2. Fernando ME et al. Influence of CYP3A5 and ABCB1 polymorphism on tacrolimus drug dosing in South Indian renal allograft recipients. Indian J Nephrol 2019;29:261-6.
3. Seibert SR et al. Tacrolimus trough and dose intra-patient variability and CYP3A5 genotype: effects on acute rejection and graft failure in European American and African American kidney transplant recipients. Clin Transplant 2018;32: e13424.
4. Liu F et al. Long-term influence of CYP3A5, CYP3A4, ABCB1, and NR1I2 polymorphisms on tacrolimus concentration in Chinese renal transplant recipients. Genet Test Mol Biomarkers 2017;21:663-73.
5. Pallet N et al. Long-term clinical impact of adaptation of initial tacrolimus dosing to CYP3A5 genotype. Am J Transplant 2016;16:2670-5.
6. Shuker N et al. A randomized controlled trial comparing the efficacy of Cyp3a5 genotype-based with body-weight-based tacrolimus dosing after living donor kidney transplantation. Am J Transplant 2016;16:2085-96.
7. De Meyer M et al. Pharmacogenetic-based strategy using de novo tacrolimus once daily after kidney transplantation: prospective pilot study. Pharmacogenomics 2016;17:1019-27.
8. Yaowakulpatana K et al. Impact of CYP3A5 polymorphism on trough concentrations and outcomes of tacrolimus minimization during the early period after kidney transplantation. Eur J Clin Pharmacol 2016;72:277-83.
9. Pulk RA et al. Multigene predictors of tacrolimus exposure in kidney transplant recipients. Pharmacogenomics 2015;16:841-54.
10. Wang L et al. Benefits of minimizing immunosuppressive dosage according to cytochrome P450 3A5 genotype in liver transplant patients: findings from a single-center study. Genet Mol Res 2015;14:3191-9.
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12. Buendia JA et al. Effects of combinational CYP3A5 6986A>G polymorphism in graft liver and native intestine on the pharmacokinetics of tacrolimus in liver transplant patients: a meta-analysis. Ther Drug Monit 2014;36:442-7.
13. Uesugi M et al. Impact of cytochrome P450 3A5 polymorphism in graft livers on the frequency of acute cellular rejection in living-donor liver transplantation. Pharmacogenet Genomics 2014;24:356-66.
14. Terrazzino S et al. The effect of CYP3A5 6986A>G and ABCB1 3435C>T on tacrolimus dose-adjusted trough levels and acute rejection rates in renal transplant patients: a systematic review and meta-analysis. Pharmacogenet Genomics 2012;22:642-5.
15. Tang HL et al. Lower tacrolimus daily dose requirements and acute rejection rates in the CYP3A5 non-expressers than expressers. Pharmacogenet Genomics 2011;21:713-20.
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17. Satoh S et al. Lack of tacrolimus circadian pharmacokinetics and CYP3A5 pharmacogenetics in the early and maintenance stages in Japanese renal transplant recipients. Br J Clin Pharmacol 2008;66:207-14.
18. Klauke B et al. No association between single nucleotide polymorphisms and the development of nephrotoxicity after orthotopic heart transplantation. J Heart Lung Transplant 2008;27:741-5.
19. Fukudo M et al. Impact of MDR1 and CYP3A5 on the oral clearance of tacrolimus and tacrolimus-related renal dysfunction in adult living-donor liver transplant patients. Pharmacogenet Genomics 2008;18:413-23.
20. Hesselink DA et al. CYP3A5 genotype is not associated with a higher risk of acute rejection in tacrolimus-treated renal transplant recipients. Pharmacogenet Genomics 2008;18:339-48.
21. Kuypers DR et al. CYP3A5 and CYP3A4 but not MDR1 single-nucleotide polymorphisms determine long-term tacrolimus disposition and drug-related nephrotoxicity in renal recipients. Clin Pharmacol Ther 2007;82:711-25.
22. Renders L et al. CYP3A5 genotype markedly influences the pharmacokinetics of tacrolimus and sirolimus in kidney transplant recipients. Clin Pharmacol Ther 2007;81:228-34.
23. Mourad M et al. The influence of genetic polymorphisms of cytochrome P450 3A5 and ABCB1 on starting dose- and weight-standardized tacrolimus trough concentrations after kidney transplantation in relation to renal function. Clin Chem Lab Med 2006;44:1192-8.
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28. Tada H et al. Impact of CYP3A5 and MDR1(ABCB1) C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. Transplant Proc 2005;37:1730-2.
29. Macphee IA et al. Tacrolimus pharmacogenetics: the CYP3A5*1 allele predicts low dose-normalized tacrolimus blood concentrations in whites and South Asians. Transplantation 2005;79:499-502.
30. Hesselink DA et al. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. Clin Pharmacol Ther 2003;74:245-54.

Date 03-02-2020

CYP3A5 homozygote expresser: tacrolimus **2357**

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 an increased conversion of tacrolimus to inactive metabolites and therefore a higher required dose.

- Indications OTHER than liver transplantation: - Use 2.5 times the initial dose that would yield the desired result in non-expressers

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:

In addition to the patient's genotype, the metabolism of tacrolimus is also determined by the genotype of the transplanted liver.
- LIVER is also of the genotype HOMOZYGOUS EXPRESSER:
- Use 2.5 times the normal initial dose
Adjustment of the dose should then be based on therapeutic drug monitoring.
- LIVER has a DIFFERENT genotype:
There is insufficient evidence in the literature to support a dose recommendation.

Literature:

1. Largeau B et al. Comparison of tacrolimus starting doses based on CYP3A5 phenotype or genotype in kidney transplant recipients. Prog Transplant 2019:1526924819873905 [Epub ahead of print].
2. Fernando ME et al. Influence of CYP3A5 and ABCB1 polymorphism on tacrolimus drug dosing in South Indian renal allograft recipients. Indian J Nephrol 2019;29:261-6.
3. Seibert SR et al. Tacrolimus trough and dose intra-patient variability and CYP3A5 genotype: effects on acute rejection and graft failure in European American and African American kidney transplant recipients. Clin Transplant 2018;32: e13424.
4. Liu F et al. Long-term influence of CYP3A5, CYP3A4, ABCB1, and NR1I2 polymorphisms on tacrolimus concentration in Chinese renal transplant recipients. Genet Test Mol Biomarkers 2017;21:663-73.
5. Pallet N et al. Long-term clinical impact of adaptation of initial tacrolimus dosing to CYP3A5 genotype. Am J Transplant 2016;16:2670-5.
6. Shuker N et al. A randomized controlled trial comparing the efficacy of Cyp3a5 genotype-based with body-weight-based tacrolimus dosing after living donor kidney transplantation. Am J Transplant 2016;16:2085-96.
7. De Meyer M et al. Pharmacogenetic-based strategy using de novo tacrolimus once daily after kidney transplantation: prospective pilot study. Pharmacogenomics 2016;17:1019-27.
8. Yaowakulpatana K et al. Impact of CYP3A5 polymorphism on trough concentrations and outcomes of tacrolimus minimization during the early period after kidney transplantation. Eur J Clin Pharmacol 2016;72:277-83.
9. Pulk RA et al. Multigene predictors of tacrolimus exposure in kidney transplant recipients. Pharmacogenomics 2015;16:841-54.
10. Wang L et al. Benefits of minimizing immunosuppressive dosage according to cytochrome P450 3A5 genotype in liver transplant patients: findings from a single-center study. Genet Mol Res 2015;14:3191-9.
11. Rojas L et al. Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. Pharmacogenomics J 2015;15:38-48.
12. Buendia JA et al. Effects of combinational CYP3A5 6986A>G polymorphism in graft liver and native intestine on the pharmacokinetics of tacrolimus in liver transplant patients: a meta-analysis. Ther Drug Monit 2014;36:442-7.
13. Uesugi M et al. Impact of cytochrome P450 3A5 polymorphism in graft livers on the frequency of acute cellular rejection in living-donor liver transplantation. Pharmacogenet Genomics 2014;24:356-66.
14. Terrazzino S et al. The effect of CYP3A5 6986A>G and ABCB1 3435C>T on tacrolimus dose-adjusted trough levels and acute rejection rates in renal transplant patients: a systematic review and meta-analysis. Pharmacogenet Genomics 2012;22:642-5.
15. Tang HL et al. Lower tacrolimus daily dose requirements and acute rejection rates in the CYP3A5 non-expressers than expressers. Pharmacogenet Genomics 2011;21:713-20.

16. Thervet E et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther 2010; 87: 721-726.
17. Satoh S et al. Lack of tacrolimus circadian pharmacokinetics and CYP3A5 pharmacogenetics in the early and maintenance stages in Japanese renal transplant recipients. Br J Clin Pharmacol 2008;66:207-14.
18. Klauke B et al. No association between single nucleotide polymorphisms and the development of nephrotoxicity after orthotopic heart transplantation. J Heart Lung Transplant 2008;27:741-5.
19. Fukudo M et al. Impact of MDR1 and CYP3A5 on the oral clearance of tacrolimus and tacrolimus-related renal dysfunction in adult living-donor liver transplant patients. Pharmacogenet Genomics 2008;18:413-23.
20. Hesselink DA et al. CYP3A5 genotype is not associated with a higher risk of acute rejection in tacrolimus-treated renal transplant recipients. Pharmacogenet Genomics 2008;18:339-48.
21. Kuypers DR et al. CYP3A5 and CYP3A4 but not MDR1 single-nucleotide polymorphisms determine long-term tacrolimus disposition and drug-related nephrotoxicity in renal recipients. Clin Pharmacol Ther 2007;82:711-25.
22. Renders L et al. CYP3A5 genotype markedly influences the pharmacokinetics of tacrolimus and sirolimus in kidney transplant recipients. Clin Pharmacol Ther 2007;81:228-34.
23. Mourad M et al. The influence of genetic polymorphisms of cytochrome P450 3A5 and ABCB1 on starting dose- and weight-standardized tacrolimus trough concentrations after kidney transplantation in relation to renal function. Clin Chem Lab Med 2006;44:1192-8.
24. Roy JN et al. Cyp3A4, Cyp3A5, and MDR-1 genetic influences on tacrolimus pharmacokinetics in renal transplant recipients. Pharmacogenet Genomics 2006;16:659-65.
25. Cheung CY et al. Influence of different allelic variants of the CYP3A and ABCB1 genes on the tacrolimus pharmacokinetic profile of Chinese renal transplant recipients. Pharmacogenomics 2006;7:563-74.
26. Uesugi M et al. Effect of intestinal CYP3A5 on postoperative tacrolimus trough levels in living-donor liver transplant recipients. Pharmacogenet Genomics 2006;16:119-27.
27. Zhang X et al. Influence of CYP3A5 and MDR1 polymorphisms on tacrolimus concentration in the early stage after renal transplantation. Clin Transplant 2005;19:638-43.
28. Tada H et al. Impact of CYP3A5 and MDR1(ABCB1) C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. Transplant Proc 2005;37:1730-2.
29. Macphee IA et al. Tacrolimus pharmacogenetics: the CYP3A5*1 allele predicts low dose-normalized tacrolimus blood concentrations in whites and South Asians. Transplantation 2005;79:499-502.
30. Hesselink DA et al. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. Clin Pharmacol Ther 2003;74:245-54.

Date 03-02-2020

CYP2D6 IM: tamoxifen **1602**

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
   Aromatase inhibitors are a possible alternative for post-menopausal women.
2. if TAMOXIFEN is selected: avoid co-medication with CYP2D6 inhibitors such as paroxetine and fluoxetine

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.
2. Martinez de Dueñas E et al. Adjusting the dose of tamoxifen in patients with early breast cancer and CYP2D6 poor metabolizer phenotype. Breast 2014;23:400-6.
3. Province MA et al. CYP2D6 genotype and adjuvant tamoxifen: meta-analysis of heterogeneous study populations. Clin Pharmacol Ther 2014;95:216-27.
4. Jung JA et al. Association between CYP2D6 genotypes and the clinical outcomes of adjuvant tamoxifen for breast cancer: a meta-analysis. Pharmacogenomics2014;15:49-60.
5. Cronin-Fenton DP et al. Metabolism and transport of tamoxifen in relation to its effectiveness: new perspectives on an ongoing controversy. Future Oncol 2014;10:107-22.
6. Lum DW et al. CYP2D6 genotype and tamoxifen response for breast cancer: a systematic review and meta-analysis. PLoS One 2013;8:e76648.
7. Zeng Z et al. CYP2D6 polymorphisms influence tamoxifen treatment outcomes in breast cancer patients: a meta-analysis. Cancer Chemother Pharmacol 2013;72:287-303.
8. Regan MM et al. CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1-98 trial. J Natl Cancer Inst 2012;104:441-51.
9. Rae JM et al. CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. J Natl Cancer Inst 2012;104:452-60.
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13. Irvin WJ Jr et al. Genotype-guided tamoxifen dosing increases active metabolite exposure in women with reduced CYP2D6 metabolism: a multicenter study. J Clin Oncol 2011;29:3232-9.
14. Lash TL et al. CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark. J Natl Cancer Inst 2011;103:489-500.
15. Thompson AM et al. Comprehensive CYP2D6 genotype and adherence affect outcome in breast cancer patients treated with tamoxifen monotherapy. Breast Cancer Res Treat 2011;125:279-87.
16. Stingl JC et al. Impact of CYP2D6 *4 genotype on progression free survival in tamoxifen breast cancer treatment. Curr Med Res Opin 2010;26:2535-42.
17. Lammers LA et al. The impact of CYP2D6-predicted phenotype on tamoxifen treatment outcome in patients with metastatic breast cancer. Br J Cancer 2010;103:765-71.
18. Schroth W et al. CYP2D6 polymorphisms as predictors of outcome in breast cancer patients treated with tamoxifen: expanded polymorphism coverage improves risk stratification. Clin Cancer Res 2010;16:4468-77.
19. Seruga B et al. Cytochrome P450 2D6 and outcomes of adjuvant tamoxifen therapy: results of a meta-analysis. Breast Cancer Res Treat 2010;122:609-17.
20. Kiyotani K et al. Lessons for pharmacogenomics studies: association study between CYP2D6 genotype and tamoxifen response. Pharmacogenet Genomics 2010;20:565-8.
21. Abraham JE et al. CYP2D6 gene variants: association with breast cancer specific survival in a cohort of breast cancer patients from the United Kingdom treated with adjuvant tamoxifen. Breast Cancer Res 2010;12:R64.
22. Schroth W et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA 2009;302:1429-36.
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24. Schroth W et al. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. J Clin Oncol 2007;25:5187-93.
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32. Wegman P et al. Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. Breast Cancer Res 2005;7:R284-90.

Date 09-11-2015

CYP2D6 PM: tamoxifen **1601**

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

Recommendation:

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

Literature:

1. Welzen ME et al. The effect of tamoxifen dose increment in patients with impaired CYP2D6 activity. Ther Drug Monit 2015;37:501-7.
2. Martinez de Dueñas E et al. Adjusting the dose of tamoxifen in patients with early breast cancer and CYP2D6 poor metabolizer phenotype. Breast 2014;23:400-6.
3. Province MA et al. CYP2D6 genotype and adjuvant tamoxifen: meta-analysis of heterogeneous study populations. Clin Pharmacol Ther 2014;95:216-27.
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14. Stingl JC et al. Impact of CYP2D6 *4 genotype on progression free survival in tamoxifen breast cancer treatment. Curr Med Res Opin 2010;26:2535-42.

15. Lammers LA et al. The impact of CYP2D6-predicted phenotype on tamoxifen treatment outcome in patients with metastatic breast cancer. Br J Cancer 2010;103:765-71.
16. Schroth W et al. CYP2D6 polymorphisms as predictors of outcome in breast cancer patients treated with tamoxifen: expanded polymorphism coverage improves risk stratification. Clin Cancer Res 2010;16:4468-77.
17. Seruga B et al. Cytochrome P450 2D6 and outcomes of adjuvant tamoxifen therapy: results of a meta-analysis. Breast Cancer Res Treat 2010;122:609-17.
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19. Abraham JE et al. CYP2D6 gene variants: association with breast cancer specific survival in a cohort of breast cancer patients from the United Kingdom treated with adjuvant tamoxifen. Breast Cancer Res 2010;12:R64.
20. Schroth W et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA 2009;302:1429-36.
21. Gjerde J et al. Effects of CYP2D6 and SULT1A1 genotypes including SULT1A1 gene copy number on tamoxifen metabolism. Ann Oncol 2008;19:56-61.
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23. Gonzalez-Santiago S et al. CYP2D6*4 polymorphism as blood predictive biomarker of breast cancer relapse in patients receiving adjuvant tamoxifen. J Clin Oncol 2007;25(18S):590.
24. Wegman P et al. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Res 2007;9:R7.
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27. Borges S et al. Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. Clin Pharmacol Ther 2006;80:61-74.
28. Goetz MP et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol 2005;23:9312-8.
29. Nowell SA et al. Association of genetic variation in tamoxifen-metabolizing enzymes with overall survival and recurrence of disease in breast cancer patients. Breast Cancer Res Treat 2005;91:249-58.
30. Jin Y et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97:30-9.
31. Wegman P et al. Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. Breast Cancer Res 2005;7:R284-90.
32. SPC Tamoxifen PCH.

Date 09-11-2015

CYP2D6 UM: tamoxifen **1603**

NO action is needed for this gene-drug interaction.

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

Literature:

1. Martinez de Dueñas E et al. Adjusting the dose of tamoxifen in patients with early breast cancer and CYP2D6 poor metabolizer phenotype. Breast 2014;23:400-6.
2. Schroth W et al. CYP2D6 polymorphisms as predictors of outcome in breast cancer patients treated with tamoxifen: expanded polymorphism coverage improves risk stratification. Clin Cancer Res 2010;16:4468-77.
3. Gjerde J et al. Effects of CYP2D6 and SULT1A1 genotypes including SULT1A1 gene copy number on tamoxifen metabolism. Ann Oncol 2008;19:56-61.
4. Lim HS et al. Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. J Clin Oncol 2007;25:3837-45.

Date 09-11-2015

DPD AS 0: tegafur **2553**

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

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

Literature:

1. Deenen MJ et al. Standard-dose tegafur combined with uracil is not safe treatment after severe toxicity from 5-fluorouracil or capecitabine. Ann Intern Med 2010;153:767-8.
2. SPC Teysuno.

Date 13-05-2019

DPD AS 1,5: tegafur **4892**

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.
  It is not possible to offer substantiated advice for dose reduction based on the literature.
  For fluorouracil and capecitabine, starting with 50 % of the standard dose is recommended and the dose should then be adjusted based on toxicity and effectiveness.
  In one study, the average dose of fluorouracil/capecitabine after titration was 64% of the standard dose for 17 patients with genotype *1/2846T and 74% of the standard dose for 51 patients with genotype *1/1236A.

Literature:

1. Cubero DI et al. Tegafur-uracil is a safe alternative for the treatment of colorectal cancer in patients with partial dihydropyrimidine dehydrogenase deficiency: a proof of principle. Ther Adv Med Oncol 2012;4:167-72.
2. Deenen MJ et al. Standard-dose tegafur combined with uracil is not safe treatment after severe toxicity from 5-fluorouracil or capecitabine. Ann Intern Med 2010;153:767-8.
3. SPC Teysuno.

Date 13-05-2019

DPD AS 1: tegafur **2554**

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.
  It is not possible to offer substantiated advice for dose reduction based on the literature.
  For fluorouracil and capecitabine, starting with 50 % of the standard dose is recommended.

Literature:

1. Cubero DI et al. Tegafur-uracil is a safe alternative for the treatment of colorectal cancer in patients with partial dihydropyrimidine dehydrogenase deficiency: a proof of principle. Ther Adv Med Oncol 2012;4:167-72.
2. Deenen MJ et al. Standard-dose tegafur combined with uracil is not safe treatment after severe toxicity from 5-fluorouracil or capecitabine. Ann Intern Med 2010;153:767-8.
3. SPC Teysuno.

Date 13-05-2019

DPD FENO: tegafur **4891**

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

- Avoid tegafur or start with a low dose and adjust the initial dose based on toxicity and efficacy
  Fluorouracil and capecitabine are not alternatives, as these are also metabolised by DPD.
  It is not possible to offer substantiated advice for dose reduction based on the literature.
  For fluorouracil and capecitabine, it is recommended to determine the residual DPD activity in mononuclear cells from peripheral blood and adjust the initial dose based on phenotype and genotype.

Literature:

1. Cubero DI et al. Tegafur-uracil is a safe alternative for the treatment of colorectal cancer in patients with partial dihydropyrimidine dehydrogenase deficiency: a proof of principle. Ther Adv Med Oncol 2012;4:167-72.
2. Deenen MJ et al. Standard-dose tegafur combined with uracil is not safe treatment after severe toxicity from 5-fluorouracil or capecitabine. Ann Intern Med 2010;153:767-8.
3. SPC Teysuno.

Date 13-05-2019

CYP2C19 IM: ticagrelor **3516**

This is NOT a gene-drug interaction.

Literature:

1. Rath PC et al. A study on the impact of CYP2C19 genotype and platelet reactivity assay on patients undergoing PCI. Indian Heart J 2015;67:114-21.
2. Steg PG et al. Stent thrombosis with ticagrelor versus clopidogrel in patients with acute coronary syndromes: an analysis from the prospective, randomized PLATO trial. Circulation 2013;128:1055-65.
3. Tantry US et al. First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: the ONSET/OFFSET and RESPOND genotype studies. Circ Cardiovasc Genet 2010;3:556-66.
4. Wallentin L et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010;376:1320-8.
5. SPC's Brilique (NL) en Brilinta (VS).

Date 19-11-2018

CYP2C19 PM: ticagrelor **3515**

This is NOT a gene-drug interaction.

Literature:

1. Zhong Z et al. Effect of cytochrome P450 2C19 polymorphism on adverse cardiovascular events after drug-eluting stent implantation in a large Hakka population with acute coronary syndrome receiving clopidogrel in southern China. Eur J Clin Pharmacol 2018;74:423-31.
2. Shen DL et al. Clinical value of CYP2C19 genetic testing for guiding the antiplatelet therapy in a Chinese population. J Cardiovasc Pharmacol 2016;67:232-6.
3. Xiong R et al. A randomized controlled trial to assess the efficacy and safety of doubling dose clopidogrel versus ticagrelor for the treatment of acute coronary syndrome in patients with CYP2C19*2 homozygotes. Int J Clin Exp Med 2015;8:13310-6.
4. Rath PC et al. A study on the impact of CYP2C19 genotype and platelet reactivity assay on patients undergoing PCI. Indian Heart J 2015;67:114-21.
5. Steg PG et al. Stent thrombosis with ticagrelor versus clopidogrel in patients with acute coronary syndromes: an analysis from the prospective, randomized PLATO trial. Circulation 2013;128:1055-65.
6. Tantry US et al. First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: the ONSET/OFFSET and RESPOND genotype studies. Circ Cardiovasc Genet 2010;3:556-66.
7. Wallentin L et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010;376:1320-8.
8. SPC's Brilique (NL) en Brilinta (VS).

Date 19-11-2018

CYP2C19 UM: ticagrelor **3517**

This is NOT a gene-drug interaction.

Literature:

1. Rath PC et al. A study on the impact of CYP2C19 genotype and platelet reactivity assay on patients undergoing PCI. Indian Heart J 2015;67:114-21.
2. Steg PG et al. Stent thrombosis with ticagrelor versus clopidogrel in patients with acute coronary syndromes: an analysis from the prospective, randomized PLATO trial. Circulation 2013;128:1055-65.
3. Tantry US et al. First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: the ONSET/OFFSET and RESPOND genotype studies. Circ Cardiovasc Genet 2010;3:556-66.

Date 19-11-2018

NUDT15 IM: tioguanine **7033**

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

- IMMUNOSUPPRESSION:
  - start with 75% of the standard dose

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

Literature:

1. Zhu Y et al. Combination of common and novel rare NUDT15 variants improves predictive sensitivity of thiopurine-induced leukopenia in children with acute lymphoblastic leukemia. Haematologica 2018 Mar 8 [Epub ahead of print].
2. Zhang AL et al. Association of NUDT15 c.415C>T allele and thiopurine-induced leukocytopenia in Asians: a systematic review and meta-analysis. Ir J Med Sci 2018;187:145-153.
3. Yi ES et al. NUDT15 variants cause hematopoietic toxicity with low 6-TGN levels in children with acute lymphoblastic leukemia. Cancer Res Treat 2017 Sep 13 [Epub ahead of print].
4. Kim H et al. APEX1 polymorphism and mercaptopurine-related early onset neutropenia in pediatric acute lymphoblastic leukemia. Cancer Res Treat 2017 Sep 4 [Epub ahead of print].
5. Chao K et al. Combined detection of NUDT15 variants could highly predict thiopurine-induced leukopenia in Chinese patients with inflammatory bowel disease: a multicenter analysis. Inflamm Bowel Dis 2017;23:1592-9.
6. Yin D et al. Impact of NUDT15 polymorphisms on thiopurines-induced myelotoxicity and thiopurines tolerance dose. Oncotarget 2017;8:13575-85.
7. Liang DC et al. NUDT15 gene polymorphism related to mercaptopurine intolerance in Taiwan Chinese children with acute lymphoblastic leukemia. Pharmacogenomics J 2016;16:536-9.
8. Zhu X et al. NUDT15 polymorphisms are better than thiopurine S-methyltransferase as predictor of risk for thiopurine-induced leukopenia in Chinese patients with Crohn's disease. Aliment Pharmacol Ther 2016;44:967-75.
9. Moriyama T et al. NUDT15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity. Nat Genet 2016;48:367-73.
10. Yang JJ et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. J Clin Oncol 2015;33:1235-42.
11. Lennard L et al. Thiopurine dose intensity and treatment outcome in childhood lymphoblastic leukaemia: the influence of thiopurine methyltransferase pharmacogenetics. Br J Haematol. 2015;169:228-40. PubMed PMID: 25441457.
12. Yang SK et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. Nat Genet 2014;46:1017-20.
13. SmPC Lanvis.

Date 04-03-2019

NUDT15 PM: tioguanine **7034**

Grade ≥ 2 leukopaenia 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:

1. Zhu Y et al. Combination of common and novel rare NUDT15 variants improves predictive sensitivity of thiopurine-induced leukopenia in children with acute lymphoblastic leukemia. Haematologica 2018 Mar 8 [Epub ahead of print].
2. Zhang AL et al. Association of NUDT15 c.415C>T allele and thiopurine-induced leukocytopenia in Asians: a systematic review and meta-analysis. Ir J Med Sci 2018;187:145-153.
3. Yi ES et al. NUDT15 variants cause hematopoietic toxicity with low 6-TGN levels in children with acute lymphoblastic leukemia. Cancer Res Treat 2017 Sep 13 [Epub ahead of print].
4. Kim H et al. APEX1 polymorphism and mercaptopurine-related early onset neutropenia in pediatric acute lymphoblastic leukemia. Cancer Res Treat 2017 Sep 4 [Epub ahead of print].
5. Chao K et al. Combined detection of NUDT15 variants could highly predict thiopurine-induced leukopenia in Chinese patients with inflammatory bowel disease: a multicenter analysis. Inflamm Bowel Dis 2017;23:1592-9.
6. Yin D et al. Impact of NUDT15 polymorphisms on thiopurines-induced myelotoxicity and thiopurines tolerance dose. Oncotarget 2017;8:13575-85.
7. Liang DC et al. NUDT15 gene polymorphism related to mercaptopurine intolerance in Taiwan Chinese children with acute lymphoblastic leukemia. Pharmacogenomics J 2016;16:536-9.
8. Zhu X et al. NUDT15 polymorphisms are better than thiopurine S-methyltransferase as predictor of risk for thiopurine-induced leukopenia in Chinese patients with Crohn's disease. Aliment Pharmacol Ther 2016;44:967-75.
9. Moriyama T et al. NUDT15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity. Nat Genet 2016;48:367-73.
10. Yang JJ et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. J Clin Oncol 2015;33:1235-42.
11. Yang SK et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. Nat Genet 2014;46:1017-20.
12. SmPC's Lanvis.

Date 04-03-2019

TPMT IM: tioguanine **1907**

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

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

1. McAtee CL et al. Treatment-related sinusoidal obstruction syndrome in children with de novo acute lymphoblastic leukemia during intensification. Cancer Chemother Pharmacol 2017;80:1261-4.
2. Lennard L et al. Thiopurine dose intensity and treatment outcome in childhood lymphoblastic leukaemia: the influence of thiopurine methyltransferase pharmacogenetics. Br J Haematol 2015;169:228-40.
3. Wray L et al. TPMT and MTHFR genotype is not associated with altered risk of thioguanine-related sinusoidal obstruction syndrome in pediatric acute lymphoblastic leukemia: a report from the Children's Oncology Group. Pediatr Blood Cancer 2014;61:2086-8.
4. Lennard L et al. The thiopurine methyltransferase genetic polymorphism is associated with thioguanine-related veno-occlusive disease of the liver in children with acute lymphoblastic leukemia. Clin Pharmacol Ther 2006;80:375-83.
5. Standen GR et al. Heterozygosity for the thiopurine methyltransferase *3A allele in an acute non-lymphoblastic leukaemia patient with delayed marrow regeneration following H-DAT chemotherapy. Br J Haematol 2001;112:1089.
6. Teml A et al. A prospective, open-label trial of 6-thioguanine in patients with ulcerative or indeterminate colitis. Scand J Gastroenterol 2005;40:1205-13.

7. Herrlinger KR et al. Thioguanine-nucleotides do not predict efficacy of tioguanine in Crohn's disease. Aliment Pharmacol Ther 2004;19:1269-76.

Date 04-11-2019

TPMT PM: tioguanine **1908**

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:

1. van der Burg M and Gerding MN. Pancytopenie bij tioguaninegebruik. Ned Tijdschr Geneeskd 2018;162:D2839.
2. Lennard L et al. Thiopurine dose intensity and treatment outcome in childhood lymphoblastic leukaemia: the influence of thiopurine methyltransferase pharmacogenetics. Br J Haematol 2015;169:228-40.
3. Wray L et al. TPMT and MTHFR genotype is not associated with altered risk of thioguanine-related sinusoidal obstruction syndrome in pediatric acute lymphoblastic leukemia: a report from the Children's Oncology Group. Pediatr Blood Cancer 2014;61:2086-8.
4. Mares WG et al. Safe 6-thioguanine therapy of a TPMT deficient Crohn's disease patient by using therapeutic drug monitoring. J Crohns Colitis 2009;3:128-30.
5. McBride KL et al. Severe 6-thioguanine-induced marrow aplasia in a child with acute lymphoblastic leukemia and inherited thiopurine methyltransferase deficiency. J Pediatr Hematol Oncol 2000;22:441-5.
6. SmPC's Lanvis (NL) and Tabloid (VS).

Date 04-11-2019

CYP2C9 IM: tolbutamide **1903**

NO action is required for this gene-drug interaction.

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

Literature:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Vormfelde SV et al. Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers. Clin Pharmacol Ther 2009;86:54-61.
3. Becker ML et al. Cytochrome P450 2C9 *2 and* 3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
4. Chen K et al. Relationship of P450 2C9 genetic polymorphisms in Chinese and the pharmacokinetics of tolbutamide. J Clin Pharm Ther 2005;30:241-9.
5. Jetter A et al. Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. Eur J Clin Pharmacol 2004;60:165-71.
6. Lee CR et al. Tolbutamide, flurbiprofen, and losartan as probes of CYP2C9 activity in humans. J Clin Pharmacol 2003;43:84-91.
7. Lee CR et al Evaluation of cytochrome P4502C9 metabolic activity with tolbutamide in CYP2C91 heterozygotes. Clin Pharmacol Ther 2002;72:562-71.
8. Shon JH et al. Effects of CYP2C19 and CYP2C9 genetic polymorphisms on the disposition of and blood glucose lowering response to tolbutamide in humans. Pharmacogenetics 2002;12:111-9.
9. Kirchheiner J et al. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. Pharmacogenetics 2002;12:101-9.

Date 20-11-2017

CYP2C9 PM: tolbutamide **1904**

NO action is required for this gene-drug interaction.

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

Literature:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Vormfelde SV et al. Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers. Clin Pharmacol Ther 2009;86:54-61.
3. Becker ML et al. Cytochrome P450 2C9 *2 and* 3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
4. Chen K et al. Relationship of P450 2C9 genetic polymorphisms in Chinese and the pharmacokinetics of tolbutamide. J Clin Pharm Ther 2005;30:241-9.
5. Jetter A et al. Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. Eur J Clin Pharmacol 2004;60:165-71.
6. Lee CR et al Evaluation of cytochrome P4502C9 metabolic activity with tolbutamide in CYP2C91 heterozygotes. Clin Pharmacol Ther 2002;72:562-71.
7. Kirchheiner J et al. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. Pharmacogenetics 2002;12:101-9.

Date 20-11-2017

CYP2C9*1/*2: tolbutamide **1898**

NO action is required for this gene-drug interaction.

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

Literature:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Vormfelde SV et al. Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers. Clin Pharmacol Ther 2009;86:54-61.
3. Becker ML et al. Cytochrome P450 2C9 *2 and* 3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
4. Jetter A et al. Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. Eur J Clin Pharmacol 2004;60:165-71.
5. Lee CR et al. Tolbutamide, flurbiprofen, and losartan as probes of CYP2C9 activity in humans. J Clin Pharmacol 2003;43:84-91.
6. Lee CR et al Evaluation of cytochrome P4502C9 metabolic activity with tolbutamide in CYP2C91 heterozygotes. Clin Pharmacol Ther 2002;72:562-71.
7. Kirchheiner J et al. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. Pharmacogenetics 2002;12:101-9.

Date 20-11-2017

CYP2C9*1/*3: tolbutamide **1899**

NO action is required for this gene-drug interaction.

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

Literature:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Vormfelde SV et al. Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers. Clin Pharmacol Ther 2009;86:54-61.
3. Becker ML et al. Cytochrome P450 2C9 *2 and* 3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
4. Chen K et al. Relationship of P450 2C9 genetic polymorphisms in Chinese and the pharmacokinetics of tolbutamide. J Clin Pharm Ther 2005;30:241-9.
5. Jetter A et al. Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. Eur J Clin Pharmacol 2004;60:165-71.
6. Lee CR et al. Tolbutamide, flurbiprofen, and losartan as probes of CYP2C9 activity in humans. J Clin Pharmacol 2003;43:84-91.
7. Lee CR et al Evaluation of cytochrome P4502C9 metabolic activity with tolbutamide in CYP2C91 heterozygotes. Clin Pharmacol Ther 2002;72:562-71.
8. Shon JH et al. Effects of CYP2C19 and CYP2C9 genetic polymorphisms on the disposition of and blood glucose lowering response to tolbutamide in humans. Pharmacogenetics 2002;12:111-9.
9. Kirchheiner J et al. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. Pharmacogenetics 2002;12:101-9.

Date 20-11-2017

CYP2C9*2/*2: tolbutamide **1900**

NO action is required for this gene-drug interaction.

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

Literature:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Becker ML et al. Cytochrome P450 2C9 *2 and* 3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
3. Jetter A et al. Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. Eur J Clin Pharmacol 2004;60:165-71.
4. Lee CR et al Evaluation of cytochrome P4502C9 metabolic activity with tolbutamide in CYP2C91 heterozygotes. Clin Pharmacol Ther 2002;72:562-71.
5. Kirchheiner J et al. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. Pharmacogenetics 2002;12:101-9.

Date 20-11-2017

CYP2C9*2/*3: tolbutamide **1901**

NO action is required for this gene-drug interaction.

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

Literature:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Vormfelde SV et al. Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers. Clin Pharmacol Ther 2009;86:54-61.
3. Becker ML et al. Cytochrome P450 2C9 *2 and* 3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
4. Kirchheiner J et al. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. Pharmacogenetics 2002;12:101-9.

Date 20-11-2017

CYP2C9*3/*3: tolbutamide **1902**

NO action is required for this gene-drug interaction.

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

Literature:

1. Swen JJ et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. Pharmacogenomics 2010;11:1517-23.
2. Vormfelde SV et al. Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers. Clin Pharmacol Ther 2009;86:54-61.
3. Becker ML et al. Cytochrome P450 2C9 *2 and* 3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288-92.
4. Chen K et al. Relationship of P450 2C9 genetic polymorphisms in Chinese and the pharmacokinetics of tolbutamide. J Clin Pharm Ther 2005;30:241-9.
5. Kirchheiner J et al. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. Pharmacogenetics 2002;12:101-9.

Date 20-11-2017

CYP2D6 IM: tramadol **1590**

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

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

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
    1. try a dose increase
    2. if this does not work: choose an alternative
       Do not select codeine, as this is also metabolised by CYP2D6.
       Morphine is not metabolised by CYP2D6.
       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:

1. Seripa D et al. Role of CYP2D6 polymorphisms in the outcome of postoperative pain treatment. Pain Med 2015;16:2012-23.
2. Dong H et al. Effect of the CYP2D6 gene polymorphism on postoperative analgesia of tramadol in Han nationality nephrectomy patients. Eur J Clin Pharmacol 2015;71:681-6.
3. Zhao Q et al. A logistic equation to determine the validity of tramadol from related gene polymorphisms and psychological factors. Pharmacogenomics 2014;15:487-95.
4. Matouskova O et al. Pupillometry in healthy volunteers as a biomarker of tramadol efficacy. J Clin Pharm Ther 2011;36:513-7.
5. Rauers NI et al. Antagonistic effects of ondansetron and tramadol? A randomized placebo and active drug controlled study. J Pain 2010;11:1274-81.
6. Kim E et al. Adverse events in analgesic treatment with tramadol associated with CYP2D6 extensive-metaboliser and OPRM1 high-expression variants. Ann Rheum Dis 2010;69:1889-90.
7. Allegaert K et al. Postmenstrual age and CYP2D6 polymorphisms determine tramadol O-demethylation in critically ill neonates and infants. Pediatr Res 2008;63:674-9.
8. Stamer UM et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007;82:41-7.
9. Slanar O et al. Miotic action of tramadol is determined by CYP2D6 genotype. Physiol Res 2007;56:129-36.
10. Wang G et al. Effect of the CYP2D6*10 C188T polymorphism on postoperative tramadol analgesia in a Chinese population. Eur J Clin Pharmacol 2006;62:927-31.
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13. Abdel-Rahman SM et al. Concordance between tramadol and dextromethorphan parent/metabolite ratios: the influence of CYP2D6 and non-CYP2D6 pathways on biotransformation. J Clin Pharmacol 2002;42:24-9.

Date 20-11-2017

CYP2D6 PM: tramadol **1589**

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

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

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
    1. try a dose increase.
    2. if this does not work: choose an alternative
       Do not select codeine, as this is also metabolised by CYP2D6.
       Morphine is not metabolised by CYP2D6.
       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:

1. Seripa D et al. Role of CYP2D6 polymorphisms in the outcome of postoperative pain treatment. Pain Med 2015;16:2012-23.
2. Matouskova O et al. Pupillometry in healthy volunteers as a biomarker of tramadol efficacy. J Clin Pharm Ther 2011;36:513-7.
3. Rauers NI et al. Antagonistic effects of ondansetron and tramadol? A randomized placebo and active drug controlled study. J Pain 2010;11:1274-81.
4. Halling J et al. CYP2D6 polymorphism in relation to tramadol metabolism: a study of faroese patients. Ther Drug Monit 2008;30:271-5.
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6. Kirchheiner J et al. Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. J Clin Psychopharmacol 2008;28:78-83.
7. Stamer UM et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007;82:41-7.
8. García-Quetglas E et al. Pharmacokinetics of tramadol enantiomers and their respective phase I metabolites in relation to CYP2D6 phenotype. Pharmacol Res 2007;55:122-30.
9. Slanar O et al. Miotic action of tramadol is determined by CYP2D6 genotype. Physiol Res 2007;56:129-36.
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11. Enggaard TP et al. The analgesic effect of tramadol after intravenous injection in healthy volunteers in relation to CYP2D6. Anesth Analg 2006;102:146-50.
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13. Borlak J et al. A rapid and simple CYP2D6 genotyping assay: case study with the analgetic tramadol. Metabolism 2003;52:1439-43.
14. Stamer UM et al. Impact of CYP2D6 genotype on postoperative tramadol analgesia. Pain 2003;105:231-8.
15. Abdel-Rahman SM et al. Concordance between tramadol and dextromethorphan parent/metabolite ratios: the influence of CYP2D6 and non-CYP2D6 pathways on biotransformation. J Clin Pharmacol 2002;42:24-9.
16. Paar WD et al. Polymorphic CYP2D6 mediates O-demethylation of the opioid analgesic tramadol. Eur J Clin Pharmacol 1997;53:235-9.
17. Poulsen L et al. The hypoalgesic effect of tramadol in relation to CYP2D6. Clin Pharmacol Ther 1996;60:636-44.
18. SPC Ultram (VS).

Date 20-11-2017

CYP2D6 UM: tramadol **1591**

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).

Literature:

1. Seripa D et al. Role of CYP2D6 polymorphisms in the outcome of postoperative pain treatment. Pain Med 2015;16:2012-23.
2. Orliaguet G et al. A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol. Pediatrics 2015;135:e753-5.
3. Saarikoski T et al. Effects of terbinafine and itraconazole on the pharmacokinetics of orally administered tramadol. Eur J Clin Pharmacol 2015;71:321-7.
4. Rauers NI et al. Antagonistic effects of ondansetron and tramadol? A randomized placebo and active drug controlled study. J Pain 2010;11:1274-81.
5. Stamer UM et al. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. Anesth Analg 2008;107:926-9.
6. Allegaert K et al. Postmenstrual age and CYP2D6 polymorphisms determine tramadol O-demethylation in critically ill neonates and infants. Pediatr Res 2008;63:674-9.
7. Kirchheiner J et al. Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. J Clin Psychopharmacol 2008;28:78-83.
8. Stamer UM et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007;82:41-7.
9. Gleason PP et al. Debilitating reaction following the initial dose of tramadol. Ann Pharmacother 1997;31:1150-2.
10. SPC Ultram (VS).

Date 20-11-2017

CYP2D6 IM: venlafaxine **1539**

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:

1. Watanabe Y et al. Factors impacting the efficacy of venlafaxine extended release 75-225 mg/day in patients with major depressive disorder: exploratory post hoc subgroup analyses of a randomized, double-blind, placebo-controlled study in Japan. Neuropsychiatr Dis Treat 2018;14:1261-72.
2. Taranu A et al. Should a routine genotyping of CYP2D6 and CYP2C19 genetic polymorphisms be recommended to predict venlafaxine efficacy in depressed patients treated in psychiatric settings? Pharmacogenomics 2017;18:639-50.
3. Berm E et al. Relation between CYP2D6 genotype, phenotype and therapeutic drug concentrations among nortriptyline and venlafaxine users in old age psychiatry. Pharmacopsychiatry 2016;49:186-190 en persoonlijke communicatie (correctie: totaal aantal patiënten met sub- and supra-therapeutische plasmaconcentraties na 3 weken waren omgewisseld in tabel 3, en het totale aantal patiënten met TDM na 3 weken was 37).
4. Jiang F et al. The influences of CYP2D6 genotypes and drug interactions on the pharmacokinetics of venlafaxine: exploring predictive biomarkers for treatment outcomes. Psychopharmacology (Berl) 2015;232:1899-909.
5. Waade RB et al. Impact of age on serum concentrations of venlafaxine and escitalopram in different CYP2D6 and CYP2C19 genotype subgroups. Eur J Clin Pharmacol 2014;70:933-40.
6. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.
7. Ng C et al. Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Hum Psychopharmacol 2013;28:516-22.
8. Van Nieuwerburgh FC et al. Response to serotonin reuptake inhibitors in OCD is not influenced by common CYP2D6 polymorphisms. Int J Psychiatry Clin Pract 2009;13:345-8.
9. Hermann M et al. Serum concentrations of venlafaxine and its metabolites O-desmethylvenlafaxine and N-desmethylvenlafaxine in heterozygous carriers of the CYP2D*6,* 4 or *5 allele. Eur J Clin Pharmacol 2008;64:483-7.
10. McAlpine DE et al. Cytochrome P450 2D6 genotype variation and venlafaxine dosage. Mayo Clin Proc 2007;82:1065-8.
11. Shams ME et al. CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. J Clin Pharm Ther 2006;31:493-502.
12. Whyte EM et al. CYP2D6 genotype and venlafaxine-XR concentrations in depressed elderly. Int J Geriatr Psychiatry 2006;21:542-9.
13. Fukuda T et al. The impact of the CYP2D6 and CYP2C19 genotypes on venlafaxine pharmacokinetics in a Japanese population. Eur J Clin Pharmacol 2000;56:175-80.
14. Veefkind AH et al. Venlafaxine serum levels and CYP2D6 genotype. Ther Drug Monit 2000;22:202-8.
15. Fukuda T et al. Effect of the CYP2D6*10 genotype on venlafaxine pharmacokinetics in healthy adult volunteers. Br J Clin Pharmacol 1999;47:450-3.

Date 04-03-2019

CYP2D6 PM: venlafaxine **1538**

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:

1. Taranu A et al. Should a routine genotyping of CYP2D6 and CYP2C19 genetic polymorphisms be recommended to predict venlafaxine efficacy in depressed patients treated in psychiatric settings? Pharmacogenomics 2017;18:639-50.
2. Berm E et al. Relation between CYP2D6 genotype, phenotype and therapeutic drug concentrations among nortriptyline and venlafaxine users in old age psychiatry. Pharmacopsychiatry 2016;49:186-190 en persoonlijke communicatie (correctie: totaal aantal patiënten met sub- and supra-therapeutische plasmaconcentraties na 3 weken waren omgewisseld in tabel 3, en het totale aantal patiënten met TDM na 3 weken was 37).
3. Waade RB et al. Impact of age on serum concentrations of venlafaxine and escitalopram in different CYP2D6 and CYP2C19 genotype subgroups. Eur J Clin Pharmacol 2014;70:933-40.
4. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.
5. Ng C et al. Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Hum Psychopharmacol 2013;28:516-22.
6. Lobello KW et al. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. J Clin Psychiatry 2010;71:1482-7.
7. Van Nieuwerburgh FC et al. Response to serotonin reuptake inhibitors in OCD is not influenced by common CYP2D6 polymorphisms. Int J Psychiatry Clin Pract 2009;13:345-8.
8. Preskorn S et al. Comparison of the pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. J Clin Psychopharmacol 2009;29:39-43.
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10. Shams ME et al. CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. J Clin Pharm Ther 2006;31:493-502.
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Date 04-03-2019

CYP2D6 UM: venlafaxine **1540**

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

1. be alert to a possible decrease in the sum of the plasma concentrations of venlafaxine and the active metabolite O-desmethylvenlafaxine
2. if necessary, increase the dose to 150% of the standard dose
3. 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 venlafaxine should be avoided
   Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline.

Literature:

1. Taranu A et al. Should a routine genotyping of CYP2D6 and CYP2C19 genetic polymorphisms be recommended to predict venlafaxine efficacy in depressed patients treated in psychiatric settings? Pharmacogenomics 2017;18:639-50.
2. Jiang F et al. The influences of CYP2D6 genotypes and drug interactions on the pharmacokinetics of venlafaxine: exploring predictive biomarkers for treatment outcomes. Psychopharmacology (Berl) 2015;232:1899-909.
3. Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81.
4. Shams ME et al. CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. J Clin Pharm Ther 2006;31:493-502.
5. Veefkind AH et al. Venlafaxine serum levels and CYP2D6 genotype. Ther Drug Monit 2000;22:202-8.

Date 04-03-2019

CYP2C19 IM: voriconazol **1683**

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

Recommendation:

- Monitor the plasma concentration

Literature:

1. Li X et al. Effect of cytochrome P450 2C19 polymorphisms on the clinical outcomes of voriconazole: a systematic review and meta-analysis. Eur J Clin Pharmacol 2016;72:1185-93.
2. Wang Y et al. Risk factors for voriconazole-associated hepatotoxicity in patients in the intensive care unit. Pharmacotherapy 2016;36:757-65.
3. Chuwongwattana S et al. A prospective observational study of CYP2C19 polymorphisms and voriconazole plasma level in adult Thai patients with invasive aspergillosis. Drug Metab Pharmacokinet 2016;31:117-22.
4. Teusink A et al. Genotype-directed dosing leads to optimized voriconazole levels in pediatric patients receiving hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2016;22:482-6.
5. Lamoureux F et al. Impact of CYP2C19 genetic polymorphisms on voriconazole dosing and exposure in adult patients with invasive fungal infections. Int J Antimicrob Agents 2016;47:124-31.
6. Chawla PK et al. Correlation of CYP2C19 genotype with plasma voriconazole levels: a preliminary retrospective study in Indians. Int J Clin Pharm 2015;37:925-30.
7. Yamada T et al. Saturated metabolism of voriconazole N-oxidation resulting in nonlinearity of pharmacokinetics of voriconazole at clinical doses. Biol Pharm Bull 2015;38:1496-503.
8. Mori M et al. Pharmacokinetics and safety of voriconazole intravenous-to-oral switch regimens in immunocompromised Japanese pediatric patients. Antimicrob Agents Chemother 2015;59:1004-13.
9. Wang T et al. Efficacy and safety of voriconazole and CYP2C19 polymorphism for optimised dosage regimens in patients with invasive fungal infections. Int J Antimicrob Agents 2014;44:436-42.
10. Liu P et al. Population pharmacokinetic-pharmacodynamic analysis of voriconazole and anidulafungin in adult patients with invasive aspergillosis. Antimicrob Agents Chemother 2014;58:4727-36.
11. Zonios D et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. J Infect Dis 2014;209:1941-8.
12. Hicks JK et al. Voriconazole plasma concentrations in immunocompromised pediatric patients vary by CYP2C19 diplotypes. Pharmacogenomics 2014;15:1065-78.
13. Kim SH et al. Clinical impact of cytochrome P450 2C19 genotype on the treatment of invasive aspergillosis under routine therapeutic drug monitoring of voriconazole in a Korean population. Infect Chemother 2013;45:406-14.
14. Racil Z et al. Monitoring trough voriconazole plasma concentrations in haematological patients: real life multicentre experience. Mycoses 2012;55:483-92.
15. Kim SH et al. Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients. Int J Infect Dis 2011;15:e753-8.
16. Berge M et al. Effect of cytochrome P450 2C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients. Eur J Clin Pharmacol 2011;67:253-60.
17. Brüggemann RJ et al. Pharmacokinetics and safety of 14 days intravenous voriconazole in allogeneic haematopoietic stem cell transplant recipients. J Antimicrob Chemother 2010;65:107-13.
18. Matsumoto K et al. Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different CYP2C19 genotypes. Int J Antimicrob Agents 2009;34:91-4.
19. Karlsson MO et al. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. Antimicrob Agents Chemother 2009;53:935-44.
20. Weiss J et al. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. J Clin Pharmacol 2009;49:196-204.
21. Levin MD et al. Hepatotoxicity of oral and intravenous voriconazole in relation to cytochrome P450 polymorphisms. J Antimicrob Chemother 2007;60:1104-7.
22. Mikus G et al. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. Clin Pharmacol Ther 2006;80:126-35.
23. Rengelshausen J et al. Opposite effects of short-term and long-term St John's wort intake on voriconazole pharmacokinetics. Clin Pharmacol Ther 2005;78:25-33.
24. Ikeda Y et al. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin Pharmacol Ther 2004;75:587-8.
25. SPC Vfend.

Date 01-05-2017

CYP2C19 PM: voriconazol **1684**

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

Recommendation:

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

Literature:

1. Li X et al. Effect of cytochrome P450 2C19 polymorphisms on the clinical outcomes of voriconazole: a systematic review and meta-analysis. Eur J Clin Pharmacol 2016;72:1185-93.
2. Wang Y et al. Risk factors for voriconazole-associated hepatotoxicity in patients in the intensive care unit. Pharmacotherapy 2016;36:757-65.
3. Chuwongwattana S et al. A prospective observational study of CYP2C19 polymorphisms and voriconazole plasma level in adult Thai patients with invasive aspergillosis. Drug Metab Pharmacokinet 2016;31:117-22.
4. Teusink A et al. Genotype-directed dosing leads to optimized voriconazole levels in pediatric patients receiving hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2016;22:482-6.
5. Lamoureux F et al. Impact of CYP2C19 genetic polymorphisms on voriconazole dosing and exposure in adult patients with invasive fungal infections. Int J Antimicrob Agents 2016;47:124-31.
6. Chawla PK et al. Correlation of CYP2C19 genotype with plasma voriconazole levels: a preliminary retrospective study in Indians. Int J Clin Pharm 2015;37:925-30.
7. Yamada T et al. Saturated metabolism of voriconazole N-oxidation resulting in nonlinearity of pharmacokinetics of voriconazole at clinical doses. Biol Pharm Bull 2015;38:1496-503.
8. Mori M et al. Pharmacokinetics and safety of voriconazole intravenous-to-oral switch regimens in immunocompromised Japanese pediatric patients. Antimicrob Agents Chemother 2015;59:1004-13.
9. Wang T et al. Efficacy and safety of voriconazole and CYP2C19 polymorphism for optimised dosage regimens in patients with invasive fungal infections. Int J Antimicrob Agents 2014;44:436-42.
10. Liu P et al. Population pharmacokinetic-pharmacodynamic analysis of voriconazole and anidulafungin in adult patients with invasive aspergillosis. Antimicrob Agents Chemother 2014;58:4727-36.
11. Zonios D et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. J Infect Dis 2014;209:1941-8.
12. Hicks JK et al. Voriconazole plasma concentrations in immunocompromised pediatric patients vary by CYP2C19 diplotypes. Pharmacogenomics 2014;15:1065-78.
13. Kim SH et al. Clinical impact of cytochrome P450 2C19 genotype on the treatment of invasive aspergillosis under routine therapeutic drug monitoring of voriconazole in a Korean population. Infect Chemother 2013;45:406-14.
14. Driscoll TA et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised adolescents and healthy adults. Antimicrob Agents Chemother 2011;55:5780-9.
15. Kim SH et al. Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients. Int J Infect Dis 2011;15:e753-8.
16. Lei HP et al. Lack of effect of Ginkgo biloba on voriconazole pharmacokinetics in Chinese volunteers identified as CYP2C19 poor and extensive metabolizers. Ann Pharmacother 2009;43:726-31.
17. Wang G et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol 2009;65:281-5.
18. Weiss J et al. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. J Clin Pharmacol 2009;49:196-204.
19. Mikus G et al. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. Clin Pharmacol Ther 2006;80:126-35.
20. Rengelshausen J et al. Opposite effects of short-term and long-term St John"s wort intake on voriconazole pharmacokinetics. Clin Pharmacol Ther 2005;78:25-33.
21. Ikeda Y et al. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin Pharmacol Ther 2004;75:587-8.
22. SPC Vfend.

Date 01-05-2017

CYP2C19 UM: voriconazol **1685**

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

Recommendation:

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

Literature:

1. Williams K et al. Association of CYP2C19 *17*/17 genotype with the risk of voriconazole-associated squamous cell carcinoma. JAMA Dermatol 2016;152:719-20.

2. Lamoureux F et al. Impact of CYP2C19 genetic polymorphisms on voriconazole dosing and exposure in adult patients with invasive fungal infections. Int J Antimicrob Agents 2016;47:124-31.
3. Chawla PK et al. Correlation of CYP2C19 genotype with plasma voriconazole levels: a preliminary retrospective study in Indians. Int J Clin Pharm 2015;37:925-30.
4. Zonios D et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. J Infect Dis 2014;209:1941-8.
5. Hicks JK et al. Voriconazole plasma concentrations in immunocompromised pediatric patients vary by CYP2C19 diplotypes. Pharmacogenomics 2014;15:1065-78.
6. Driscoll TA et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised children and healthy adults. Antimicrob Agents Chemother 2011;55:5770-9.
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8. Berge M et al. Effect of cytochrome P450 2C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients. Eur J Clin Pharmacol 2011;67:253-60.
9. Wang G et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol 2009;65:281-5.
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11. Li X et al. Effect of cytochrome P450 2C19 polymorphisms on the clinical outcomes of voriconazole: a systematic review and meta-analysis. Eur J Clin Pharmacol 2016;72:1185-93.

Date 01-05-2017

CYP2C9 IM: warfarine **6233**

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. Algorithms for Caucasian patients usually contain only the *2 and *3 allele. If the activity of the reduced-activity alleles is comparable to the activity of *2 or *3, then the algorithm can be completed as if *1/*2 or *1/*3 is present. See https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/medicatiebewaking-g-standaard/background-information-pharmacogenetics for Excel files containing calculation modules for oral and equivalent intravenous doses. From day 6 on the standard algorithm without genotype information can be used to calculate the dose.
Modified dose algorithms have been developed for patients of African or (East) Asian heritage.

Literature:

1. Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis 2015; 39:228-34.
2. Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. Int J Cardiol 2014; 177:654-7.
3. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014; 12:1480-7.
4. Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014; 174:1330-8.
5. Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013; 168:4234-43.
6. Jorgensen AL et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012; 7:e44064.
7. Lindh JD et al. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. Eur J Clin Pharmacol 2009; 65:365-75.
8. Sanderson S et al. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005; 7:97-104.
9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9 PM: warfarine **6234**

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

Literature:

1. Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis 2015; 39:228-34.
2. Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. Int J Cardiol 2014; 177:654-7.
3. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014; 12:1480-7.
4. Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014; 174:1330-8.
5. Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013; 168:4234-43.
6. Jorgensen AL et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012; 7:e44064.
7. Lindh JD et al. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. Eur J Clin Pharmacol 2009; 65:365-75.
8. Sanderson S et al. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005; 7:97-104.
9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9*1/*2: warfarine **6228**

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:

1. Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis 2015; 39:228-34.
2. Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. Int J Cardiol 2014; 177:654-7.
3. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014; 12:1480-7.
4. Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014; 174:1330-8.
5. Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013; 168:4234-43.
6. Jorgensen AL et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012; 7:e44064.
7. Lindh JD et al. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. Eur J Clin Pharmacol 2009; 65:365-75.
8. Sanderson S et al. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005; 7:97-104.
9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9*1/*3: warfarine **6229**

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:

1. Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis 2015; 39:228-34.
2. Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. Int J Cardiol 2014; 177:654-7.
3. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014; 12:1480-7.
4. Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014; 174:1330-8.
5. Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013; 168:4234-43.
6. Jorgensen AL et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012; 7:e44064.
7. Lindh JD et al. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. Eur J Clin Pharmacol 2009; 65:365-75.
8. Sanderson S et al. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005; 7:97-104.
9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9*2/*2: warfarine **6230**

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:

1. Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis 2015; 39:228-34.
2. Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. Int J Cardiol 2014; 177:654-7.
3. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014; 12:1480-7.
4. Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014; 174:1330-8.
5. Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013; 168:4234-43.
6. Jorgensen AL et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012; 7:e44064.
7. Lindh JD et al. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. Eur J Clin Pharmacol 2009; 65:365-75.
8. Sanderson S et al. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005; 7:97-104.
9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9*2/*3: warfarine **6231**

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:

1. Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis 2015; 39:228-34.
2. Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. Int J Cardiol 2014; 177:654-7.
3. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014; 12:1480-7.
4. Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014; 174:1330-8.
5. Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013; 168:4234-43.
6. Jorgensen AL et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012; 7:e44064.
7. Lindh JD et al. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. Eur J Clin Pharmacol 2009; 65:365-75.
8. Sanderson S et al. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005; 7:97-104.
9. SPC Coumadin (VS).

Date 24-08-2016

CYP2C9*3/*3: warfarine **6232**

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:

1. Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis 2015; 39:228-34.
2. Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. Int J Cardiol 2014; 177:654-7.
3. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014; 12:1480-7.
4. Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014; 174:1330-8.
5. Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013; 168:4234-43.
6. Jorgensen AL et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012; 7:e44064.
7. Lindh JD et al. Influence of CYP2C9 genotype on warfarin dose requirements--a systematic review and meta-analysis. Eur J Clin Pharmacol 2009; 65:365-75.
8. Sanderson S et al. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005; 7:97-104.
9. SPC Coumadin (VS).

Date 24-08-2016

VKORC1 -1639 AA: warfarine **6236**

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:

1. Zhang J et al. The influence of VKORC1 gene polymorphism on warfarin maintenance dosage in pediatric patients: A systematic review and meta-analysis. Thromb Res 2015;136:955-61.
2. Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis 2015;39:228-34.
3. Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmaco-genetic dosing of warfarin. Int J Cardiol 2014;177:654-7.
4. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014;12:1480-7.
5. Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014;174:1330-8.
6. Jin B et al. The impact of VKORC1-1639G > A genetic polymorphism upon warfarin dose requirement in different ethnic populations. Curr Med Res Opin 2014;30:1505-11.
7. Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013;168:4234-43.
8. Jorgensen AL et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012;7:e44064.
9. Yang L et al. Impact of VKORC1 gene polymorphism on interindividual and interethnic warfarin dosage requirement--a systematic review and meta analysis. Thromb Res 2010;125:e159-66.
10. SPC Coumadin (VS).

Date 24-08-2016

VKORC1 -1639 GA: warfarine **6235**

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:

1. Zhang J et al. The influence of VKORC1 gene polymorphism on warfarin maintenance dosage in pediatric patients: A systematic review and meta-analysis. Thromb Res 2015;136:955-61.
2. Liao Z et al. Meta-analysis of randomized controlled trials reveals an improved clinical outcome of using genotype plus clinical algorithm for warfarin dosing. J Thromb Thrombolysis 2015;39:228-34.
3. Xu H et al. Meta-analysis of efficacy and safety of genotype-guided pharmacogenetic dosing of warfarin. Int J Cardiol 2014;177:654-7.
4. Franchini M et al. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost 2014;12:1480-7.
5. Stergiopoulos K et al. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. JAMA Intern Med 2014;174:1330-8.
6. Jin B et al. The impact of VKORC1-1639G > A genetic polymorphism upon warfarin dose requirement in different ethnic populations. Curr Med Res Opin 2014;30:1505-11.
7. Yang J et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: a systematic review and meta-analysis. Int J Cardiol 2013;168:4234-43.
8. Jorgensen AL et al. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and meta-analysis. PLoS One 2012;7:e44064.
9. SPC Coumadin (VS).

Date 24-08-2016

CYP2D6 IM: zuclopentixol **1548**

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:

1. Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84.
2. Van Berlo-van de Laar et al. Dosering aanpassen aan eliminatiesnelheid. Pharm Weekblad 2004; 139:740-43.
3. Jaanson P et al. Maintenance therapy with zuclopentixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype. Psychopharmacology 2002;162:67-73.
4. Jerling M et al. The CYP2D6 genotype predicts the oral clearance of the neuroleptic agents perphenazine and zuclopentixol. Clin Pharmacol Ther 1996;59:423-8.
5. SmPC Cisordinol.

Date 14-09-2020

CYP2D6 PM: zuclopentixol **1547**

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 1.7-fold higher.

- use 50% of the standard dose

Literature:

1. Van Berlo-van de Laar et al. Dosering aanpassen aan eliminatiesnelheid. Pharm Weekblad 2004; 139:740-43.
2. Jaanson P et al. Maintenance therapy with zuclopentixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype. Psychopharmacology 2002;162:67-73.
3. Linnet K et al. Influence of Cyp2D6 genetic polymorphism on ratios of steady-state serum concentration to dose of the neuroleptic zuclopentixol. Ther Drug Monit 1996;18:629-34.
4. Jerling M et al. The CYP2D6 genotype predicts the oral clearance of the neuroleptic agents perphenazine and zuclopentixol. Clin Pharmacol Ther 1996;59:423-8.
5. Dahl ML et al. Disposition of the neuroleptic zuclopentixol cosegregates with the polymorphic hydroxylation of debrisoquine in humans. Acta Psychiatr Scand 1991;84:99-102.
6. SmPC Cisordinol.

Date 14-09-2020

CYP2D6 UM: zuclopentixol **1549**

The risk of ineffectiveness may be elevated. The genetic variation leads to an increased conversion of zuclopentixol, which causes the plasma concentration to be approximately 33% lower.

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

Literature:

1. Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84.
2. SmPC Cisordinol.

Date 14-09-2020
