



## Voriconazole Therapy and *CYP2C19* Genotype

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### Introduction

Voriconazole (brand name Vfend) is a broad-spectrum antifungal agent used to treat invasive fungal infections (IFI). Invasive fungal infections are an important cause of morbidity and mortality in critically ill children and immunocompromised individuals.

Voriconazole is a triazole and is the first line treatment of invasive aspergillosis. It is also licensed to treat candidemia (in individuals who do not have neutropenia), disseminated candidiasis, and esophageal candidiasis. For serious fungal infections caused by *Scedosporium* and *Fusarium* species, voriconazole may be used in those who are unable to take, or have not responded to, other therapy (1).

Therapeutic drug monitoring of voriconazole has become the standard of care to ensure efficacy and avoid adverse effects (2, 3). Low serum voriconazole concentrations have been associated with treatment failure, which may have devastating consequences in individuals who are seriously ill with an invasive infection. High serum voriconazole concentrations are associated with adverse effects, such as neurotoxicity.

Interindividual drug serum concentrations vary widely among individuals treated with a dose of voriconazole, which is due in part to genetic variation in the *CYP2C19* gene. Voriconazole is primarily metabolized by the *CYP2C19* enzyme, with contributions by *CYP2C9* and *CYP3A4*.

Individuals who lack *CYP2C19* activity (“*CYP2C19* poor metabolizers”) have, on average, 4-fold higher voriconazole exposure than normal metabolizers (Table 1). In contrast, individuals who have increased *CYP2C19* activity (“rapid” and “ultrarapid metabolizers”) have lower serum concentrations of voriconazole (1, 4). Genetic tests are currently available for the [voriconazole response](#) and the [CYP2C19 gene](#).

The FDA-approved drug label for voriconazole discusses the influence of *CYP2C19* on drug levels but does not provide specific dosing recommendations based on the *CYP2C19* metabolizer status (Table 1). The label currently only incorporates the type of infection and the individuals weight into the dosing guidelines (1).

However, dosing recommendations for voriconazole based on *CYP2C19* metabolizer type are available from the Dutch Pharmacogenetics Working Group (DPWG, Table 2) and the Clinical Pharmacogenetics Implementation Consortium (CPIC, Table 3) (4, 5).

**Table 1.** FDA (2019) Drug Label for Voriconazole Therapeutic Recommendations based on *CYP2C19* Genotype

Phenotype	Voriconazole
CYP2C19 poor metabolizers	Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC <sub>τ</sub> ) than their homozygous normal metabolizer counterparts. Subjects who are heterozygous normal metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous normal metabolizer counterparts

Please see Therapeutic Recommendations based on Genotype for more information from the FDA. This table is adapted from (1).

**Table 2.** DPWG (2019) Recommendations for Voriconazole and *CYP2C19* Genotype

Phenotype	Recommendations
CYP2C19 poor metabolizers	Use 50% of the standard dose and monitor the plasma concentration.
CYP2C19 intermediate metabolizers	Monitor the plasma concentration.
CYP2C19 ultrarapid metabolizers	Use an initial dose that is 1.5x higher and monitor the plasma concentration.

Please see Therapeutic Recommendations based on Genotype for more information from DPWG. This table is adapted from (5).

**Table 3.** CPIC (2016) Dosing Recommendations for Voriconazole Treatment based on *CYP2C19* Phenotype for Adults

CYP2C19 phenotype	Implications for voriconazole pharmacologic measures	Therapeutic recommendations	Classification of recommendations <sup>a</sup>
CYP2C19 ultrarapid metabolizer (*17/*17)	In individuals for whom an ultrarapid metabolizer genotype (*17/*17) is identified, the probability of attainment of therapeutic voriconazole concentrations is small with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole. <sup>b</sup>	Moderate <sup>c</sup>
CYP2C19 rapid metabolizer (*1/*17)	In individuals for whom a rapid metabolizer genotype (*1/*17) is identified, the probability of attainment of therapeutic concentrations is modest with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole. <sup>b</sup>	Moderate
CYP2C19 normal metabolizer	Normal voriconazole metabolism	Initiate therapy with recommended standard of care dosing. <sup>b</sup>	Strong
CYP2C19 intermediate metabolizer	Higher dose-adjusted trough concentrations of voriconazole compared with normal metabolizers	Initiate therapy with recommended standard of care dosing. <sup>b</sup>	Moderate

Table 3. continued from previous page.

CYP2C19 phenotype	Implications for voriconazole pharmacologic measures	Therapeutic recommendations	Classification of recommendations <sup>a</sup>
CYP2C19 poor metabolizer	Higher dose-adjusted trough concentrations of voriconazole and may increase probability of adverse events	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole. <sup>b</sup> In the event that voriconazole is considered to be the most appropriate agent, based on clinical advice, for an individual with poor metabolizer genotype, voriconazole should be administered at a preferably lower than standard dose with careful therapeutic drug monitoring.	Moderate

<sup>a</sup> Rating scheme is described in Supplementary Data online (4).

<sup>b</sup> Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, species, site of infection, therapeutic drug monitoring, and comorbidities.

<sup>c</sup> Recommendations based upon data extrapolated from individuals with CYP2C19\*1/\*17 genotype.

Please see Therapeutic Recommendations based on Genotype for more information from CPIC. This table is adapted from (4).

## Drug: Voriconazole

Voriconazole is a broad-spectrum antifungal agent that belongs to the drug class of triazole antifungals. There currently are 5 triazole antifungal drugs licensed for use in the United States: fluconazole, isavuconazole, itraconazole, posaconazole, and voriconazole. These medications vary in how they are administered, the pathogens they target, and their side effects (6).

Compared with other triazole antifungals, voriconazole has enhanced activity against the *Aspergillus* species, and similar to other triazole antifungals, voriconazole is active against the *Candida* species. The Infectious Diseases Society of America recommend voriconazole as the first-line therapy for invasive aspergillosis, and as an alternative therapy for candidemia, in individuals who do not have neutropenia (4, 7).

Voriconazole is also used to treat esophageal candidiasis, disseminated candidiasis (in skin, abdomen, kidney, bladder wall, and wounds), and serious infections caused by *Scedosporium apiospermum* complex and *Fusarium* species, including *Fusarium solani* in individuals intolerant of, or refractory to, other therapy (1).

A healthy adult has an immune system that can prevent a fungal infection becoming invasive and disseminating. But IFI can be life threatening in adults who have a weakened immune system. Susceptible individuals may be at the extremes of age (very young, or elderly), or be immunocompromised because of a disease or its treatment (e.g., cancer, chemotherapy, immunosuppression following transplant surgery). Genetic conditions may also cause immunodeficiency. For these individuals, early treatment of IFI is associated with increased survival (3, 8, 9).

Triazoles share a similar mechanism of action – they disrupt the synthesis of ergosterol, an important part of the fungal cell membrane. They do this by inhibiting the fungal enzyme that produces ergosterol (lanosterol 14- $\alpha$ -demethylase). The damaged fungal cell membrane becomes more permeable, resulting in cell lysis and death.

Triazoles are generally well tolerated but they have a narrow therapeutic index. Gastrointestinal symptoms are most frequently reported, including nausea, abdominal pain, vomiting, and diarrhea. All triazoles have been

associated with liver dysfunction and hepatotoxicity. Therefore, careful monitoring of liver enzymes is recommended for everyone receiving triazole therapy (6).

Voriconazole can cause fetal harm and should not be used during pregnancy unless the benefit to the mother outweighs the risk to the fetus. In animal studies, voriconazole was associated with teratogenicity (abnormal development of the embryo), embryo toxicity, and death. If voriconazole is used during pregnancy, or if the individual becomes pregnant while taking voriconazole, they should be informed of the potential hazards to the fetus.

Adverse effects specifically associated with voriconazole therapy include vision changes (e.g., photopsia – flashes of light, and photophobia – increased sensitivity to light), periostitis (inflammation of the periosteum that surrounds bones), and neurological toxicity (e.g., visual hallucinations, encephalopathy, and neuropathy).

Clinically, it is important to distinguish between vision changes, which tend to be minor and reversible, and visual hallucinations, which may be one of the first indications of severe neurotoxicity.

Voriconazole can be administered orally or by IV, and a loading dose is given at the start of therapy. For the treatment of invasive aspergillosis in adults, an IV loading dose of 6 mg/kg every 12 hours for 2 doses is recommended, followed by an IV maintenance dose of 4 mg/kg every 12 hours. Intravenous treatment should be continued for at least 7 days. After the individual has improved clinically, oral voriconazole can be used instead of IV (recommended maintenance dose of 200 mg every 12 hours).

The voriconazole drug label states that dose adjustment may be indicated for cases of non-response (dose increased), for individuals who cannot tolerate the medication, have liver insufficiency, or for adults who weigh less than 40 kg (dose decreased). The dose may also need to be adjusted based on concurrent therapy, as many drugs (particularly those that inhibit or induce CYP3A4, CYP2C9, or CYP2C19) can lead to altered voriconazole levels (1).

The dosing of voriconazole is further complicated by the elimination of the drug being characterized by “non-linear pharmacokinetics”. Pharmacokinetics is the study of the movement of drugs in the body, including the processes of absorption, distribution, metabolism, and excretion. The term “linear pharmacokinetics” refers to a graph that shows a straight line when various factors are plotted e.g., the dose of the drug versus the serum concentration of the drug. For voriconazole, the observed “non-linear” pharmacokinetics means that above a certain drug dose, the concentration of the drug in the serum increases disproportionately. This occurs because the enzymes responsible for metabolizing and eliminating voriconazole become saturated (e.g., CYP2C19), (10).

In children, however, voriconazole has been found to show linear pharmacokinetics over a wider range of drug doses. This is thought to be because children have a higher expression of CYP2C19, and therefore an increased capacity to metabolize voriconazole. This means that children will often require higher doses to achieve therapeutic drug concentrations (3, 11).

There is substantial variability in voriconazole serum drug concentrations among individuals receiving standard doses of voriconazole. This is in part due to non-linear kinetics and other factors listed above (liver function, comorbidities, concurrent medications, age of the individual), as well as the presence of inflammation, and interindividual pharmacogenetic variability (12, 13).

Genetic variants in the *CYP2C19* gene play an important role in voriconazole serum concentration variability. Voriconazole is metabolized primarily by CYP2C19, and to a lesser extent by CYP3A4 and CYP2C9. Individuals who lack CYP2C9 activity (up to 20% of individuals of Asian descent and 3-5% in many other populations, Table 4) will have a higher exposure to voriconazole in response to standard doses, and are at a higher risk of adverse effects (3, 4, 9). Genetic variation in the *CYP3A4* gene may also influence voriconazole pharmacokinetics (14-17).

Therapeutic drug monitoring of voriconazole has now become the standard of care in many medical centers to improve treatment efficacy and avoid toxicity. However, if an individual's *CYP2C19* status is known, sub- and supratherapeutic voriconazole concentrations can potentially be avoided in individuals vulnerable to severe infections. Voriconazole dosing recommendations based on *CYP2C19* genotype and/or phenotype have been published by CPIC and DPWG (see Therapeutic Recommendations based on Genotype). (2, 4, 5, 18-23).

Although the FDA drug label states voriconazole is indicated for individuals aged 12 years and above, voriconazole is used in children with IFI, and the label discusses pediatric use. As such, CPIC have provided therapeutic recommendations for the use of voriconazole based on *CYP2C19* genotype for pediatric individuals (children and adolescents less than 18 years old) (1, 4).

## Gene: CYP2C19

The cytochrome P450 (CYP) superfamily is a large and diverse group of hepatic enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The CYP genes are very polymorphic and can result in reduced, absent, or increased drug metabolism.

The CYP2C19 enzyme contributes to the metabolism of a range of clinically important drugs, such as antidepressants, benzodiazepines, antiplatelet agents, some proton pump inhibitors, and antifungal agents such as voriconazole.

The *CYP2C19* gene is highly polymorphic, as there are currently 35 variant star (\*) alleles cataloged by the Pharmacogene Variation (PharmVar) Consortium. The *CYP2C19\*1* is considered the wild-type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype.

The *CYP2C19\*17* allele is associated with increased enzyme activity and is found among individuals with 'rapid' (*\*1/\*17*) and 'ultrarapid' (*\*17/\*17*) metabolizer phenotypes. Heterozygous carriers of non-functional alleles (e.g., *\*2* and *\*3*) are classified as 'intermediate metabolizers' (e.g., *\*1/\*2*), and individuals who have 2 non-functional alleles are classified as "poor metabolizers" (e.g., *\*2/\*2*, *\*2/\*3*) (Table 4).

**Table 4.** CPIC (2016). Assignment of CYP2C19 Phenotype based on Genotype.

Phenotype	Genotype	Examples of diplotypes
CYP2C19 ultrarapid metabolizer (approximately 2–5% of individuals) <sup>a</sup>	An individual with 2 increased function alleles	<i>*17/*17</i>
CYP2C19 rapid metabolizer (approximately 2–30% of individuals)	An individual with one normal function allele and one increased function allele	<i>*1/*17</i>
CYP2C19 normal metabolizer (approximately 35–50% of individuals)	An individual with 2 normal function alleles	<i>*1/*1</i>
CYP2C19 intermediate metabolizer (approximately 18–45% of individuals)	An individual with one normal function allele and one no function allele or one no function allele and one increased function allele	<i>*1/*2</i> <i>*1/*3</i> <i>*2/*17<sup>b</sup></i>
CYP2C19 poor metabolizer (approximately 2–15% of individuals)	An individual with 2 no function alleles	<i>*2/*2</i> <i>*2/*3</i> <i>*3/*3</i>

<sup>a</sup> CYP2C19 metabolizer status frequencies are based on average multi-ethnic frequencies. See the *CYP2C19* Frequency Tables for population-specific allele and phenotype frequencies (4).

<sup>b</sup> The predicted metabolizer phenotype for the *\*2/\*17* genotype is a provisional classification. The currently available evidence indicates that the *CYP2C19\*17* increased function allele is unable to completely compensate for the *CYP2C19\*2* no function allele. This CPIC table is adapted from (4).

Approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese are *CYP2C19* poor metabolizers, and up to 45% of individuals are *CYP2C19* intermediate metabolizers (19).

The most common no function allele is *CYP2C19\*2*, which is defined by a c.681G>A variant in exon 5 that creates an aberrant splice site that translates a truncated and non-functioning protein. The *CYP2C19\*2* allele frequencies are ~15% in Caucasians and Africans, and ~29–35% in Asians (24).

Another commonly tested no function allele is *CYP2C19\*3*, which is defined by a c.636G>A variant in exon 4 that creates a premature stop codon. The *CYP2C19\*3* allele frequencies are ~2-9% in Asian populations, but rare in other racial groups. Other no function variants occur in less than 1% of the general population, and include *CYP2C19\*4-8* (24).

The *CYP2C19\*17* allele is an increased function allele characterized by a promoter variant that results in increased gene expression, and is commonly tested for with an allele frequency of 4-21%.

## Linking Gene Variation with Treatment Response

Although studies have not consistently found an association between the *CYP2C19* genotype and the toxicity or efficacy of voriconazole, *CYP2C19* genotype does contribute to the variation observed in voriconazole pharmacokinetics and potentially, could be used to guide the initial dose selection (25, 26).

The presence of *CYP2C19* variants can lead to increased or decreased voriconazole serum concentrations (27, 28). Low concentrations of voriconazole are associated with treatment failure. High concentrations are not associated with an increase in efficacy but are associated with serious adverse effects such as neurotoxicity (2, 4).

## CYP2C19 Poor Metabolizers

Individuals who are *CYP2C19* poor metabolizers have increased serum voriconazole concentrations, which are up to 4 times higher than normal *CYP2C19* metabolizers. However, this difference is most marked in healthy volunteers – studies with patients have found conflicting results, most likely due to factors such as drug interactions, other conditions, and organ dysfunction (2, 3).

Several studies have found that increased voriconazole serum concentrations are associated with increased risk of side effects, including hepatotoxicity, visual hallucinations and encephalopathy (4, 18, 29-32). The FDA confirms that *CYP2C19* poor metabolizers have higher exposure to voriconazole, but the label does not discuss alternative dosing based on *CYP2C19* metabolizer status. However, dosing guidelines based on *CYP2C19* genotype have been published by CPIC and DPWG.

Therapeutic recommendations from CPIC for *CYP2C19* poor metabolizers include choosing an alternative agent that is not dependent upon *CYP2C19* metabolism, or if there is a strong case for using voriconazole, use a lower dose than standard with careful therapeutic drug monitoring. For all genotypes, CPIC recommend bearing in mind that further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, fungal species, site of infection, therapeutic drug monitoring, and comorbidities (Table 3) (4).

For *CYP2C19* poor metabolizers, the DPWG recommend using 50% of the standard dose, again with careful monitoring (see Therapeutic Recommendations based on Genotype) (4, 5).

## CYP2C19 Intermediate Metabolizers

Data are lacking for *CYP2C19* intermediate metabolizers, therefore CPIC recommend following the standard dosing regimen, with therapeutic drug monitoring. The DPWG also recommends the standard dose with therapeutic drug monitoring (4, 5).



## CYP2C19 Rapid and Ultrarapid Metabolizers

Trough concentrations of voriconazole can predict the clinical response, with low levels associated with a lower response rate and treatment failure (18, 30, 31, 33-35). Low levels of voriconazole are found in individuals who are *CYP2C19* rapid (individuals who have one copy of *CYP2C19\*17*) or ultrarapid (individuals who have 2 copies of *CYP2C19\*17*) metabolizers. Several studies have found that the *CYP2C19\*17* allele is associated with subtherapeutic voriconazole concentrations (2, 27, 36-38).

For these individuals, attempting to achieve therapeutic drug levels may be unsuccessful, or cause serious delays, allowing the invasive fungal disease to progress (3).

For *CYP2C19* rapid and ultrarapid metabolizers, CPIC recommends an alternative antifungal agent that is not dependent on *CYP2C19* metabolism, whereas the DPWG recommends using an initial dose of voriconazole that is 1.5 times higher than the standard dose, with therapeutic drug monitoring (Table 3, Therapeutic Recommendations based on Genotype) (4, 5).

## Genetic Testing

Clinical genotyping tests are available for several *CYP2C19* alleles. The NIH's Genetic Testing Registry (GTR) provides examples of the genetic tests that are currently available for the [voriconazole response](#) and the [CYP2C19 gene](#). In addition, variant *CYP2C19* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (39).

Usually an individual's result is reported as a diplotype, such as *CYP2C19 \*1/\*1*, and may also include an interpretation of the predicted metabolizer phenotype (ultrarapid, normal, intermediate, or poor). Table 4 summarizes common *CYP2C19* phenotypes.

## Therapeutic Recommendations based on Genotype

**This section contains excerpted<sup>1</sup> information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.**

### 2019 Statement from the US Food and Drug Administration (FDA)

*CYP2C19*, significantly involved in the metabolism of voriconazole, exhibits genetic polymorphism. Approximately 15 to 20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3 to 5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure ( $AUC_{\tau}$ ) than their homozygous normal metabolizer counterparts. Subjects who are heterozygous normal metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous normal metabolizer counterparts.

**Please review the complete therapeutic recommendations that are located here: (1)**

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<sup>1</sup> The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

## 2019 Statement from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

### CYP2C19 Poor Metabolizers

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

### CYP2C19 Intermediate Metabolizers

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

### CYP2C19 Ultrarapid metabolizers

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

### Background information

Mechanism:

Voriconazole is predominantly metabolised by CYP2C19 and otherwise by CYP2C9 and CYP3A4. The most important metabolite, voriconazole-N-oxide, is inactive.

For more information about CYP2C19 phenotypes: see the general background information about CYP2C19 on the KNMP Knowledge Bank or on [www.knmp.nl](http://www.knmp.nl) (search for key word "CYP2C19").

### Other considerations:

Several studies indicate a higher risk of hepatotoxicity at higher plasma concentrations of voriconazole. However, the relationship between the plasma concentration and the effect or side effects (hepatotoxicity) has not been clearly identified.

The kinetics of voriconazole are non-linear at therapeutic doses.

**Please review the complete therapeutic recommendations that are located here: ( 5 ).**

## 2016 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Clinical studies have not consistently demonstrated an association between CYP2C19 genotype and adverse reactions. However, as individual patients who are poor metabolizers may have elevated levels leading to toxicity, the use of another antifungal agent is recommended. Under circumstances in which voriconazole is strongly indicated for treatment of an invasive mycosis in a patient with a poor metabolizer phenotype, administration of a lower dosage with meticulous therapeutic drug monitoring may be feasible (Table 3).

Knowledge of CYP2C19 ultrarapid and rapid metabolizer genotypes may prevent subtherapeutic concentrations of voriconazole that may lead to treatment failure. In such cases, an alternative antifungal agent also is



recommended, especially as several case reports have documented voriconazole treatment failure in *CYP2C19* ultrarapid metabolizers (see Supplementary Table S1 online). Attempting to obtain therapeutic levels in patients with ultrarapid metabolizer genotypes are often unsuccessful. Serious delays in achieving therapeutic concentrations in such patients with active invasive mycoses may result in disease progression.

Several alternative agents may be used instead of voriconazole for treatment of invasive mold infections. These include isavuconazole, lipid formulations of amphotericin B, and posaconazole (Table 3). The antifungal triazole isavuconazole is approved for the primary treatment of invasive aspergillosis and invasive mucormycosis and is available in intravenous and oral dosage forms. As isavuconazole is a substrate of *CYP3A4*, variant alleles in this gene are unlikely to affect its clearance. Only limited data for isavuconazole are currently available in the pediatric population. Liposomal amphotericin B is an alternative therapy to voriconazole for the primary treatment of invasive aspergillosis. Posaconazole is currently indicated for salvage therapy of invasive aspergillosis. The recently approved posaconazole delayed release and intravenous dosage forms achieve higher concentrations than that of the posaconazole suspension. However, intravenous posaconazole requires administration via a central line due to phlebitis with peripheral administration. Similar to voriconazole, intravenous posaconazole also contains the solubilizer sulfobutylether-beta-cyclodextrin sodium. Posaconazole is cleared largely as unchanged compound with <20% of compound being excreted as a glucuronide conjugate. Uridine 50-diphospho- glucuronosyltransferase glucuronidation of posaconazole is not significantly affected by genetic variation. Administration of posaconazole should still be guided by TDM.

**Please review the complete therapeutic recommendations that are located here: (4).**

## Nomenclature for selected *CYP2C19* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
<i>CYP2C19</i> *2	681G>A Pro227Pro	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
<i>CYP2C19</i> *3	636G>A Trp212Ter	NM_000769.1:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
<i>CYP2C19</i> *17	-806C>T	NM_000769.1:c.-806C>T	Not applicable - variant occurs in a non-coding region	rs12248560

dbSNP: The Single Nucleotide Polymorphism Database

Note: the normal “wild-type” allele is *CYP2C19*\*1.

Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (40).

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).

Nomenclature for cytochrome P450 enzymes is available from Pharmacogene Variation (PharmVar) Consortium.

Please note that the *CYP2C19*\*2 defining variant (rs4244285) has recently been reported to be in high linkage disequilibrium with an intronic variant implicated in aberrant slicing (rs12769205) (41).

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Research, Director, Pediatric Clinical Pharmacology, Department of Pediatrics, Wright State University Boonshoft School of Medicine, Dayton Children's Hospital, Dayton (OH), USA.

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