

## Original Article



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### Conflict of Interest

No conflicts of interest.

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# Pharmacokinetics and Safety of Two Voriconazole Formulations after Intravenous Infusion in Healthy Korean Volunteers

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## ABSTRACT

**Background:** Voriconazole, a triazole antifungal agent exhibits broad-spectrum antifungal activity. It is used to treat severe, invasive fungal infections, including invasive aspergillosis and candidemia. The aim of this study was to assess the pharmacokinetic equivalence of a test formulation (Vorico® Injection) and reference formulation (Vfend® IV) of voriconazole.

**Materials and Methods:** This was a randomized, open-label, single-dose, three-group, two-treatment, two-sequence, two-period, crossover phase I trial with 7-day washout periods (ClinicalTrials.gov identifier NCT02631954). Twenty-four healthy Korean male subjects were recruited. In each group, eight subjects were randomized in a 1:1:1 manner to receive a single dose of 200 mg test or reference formulation intravenously over 1.5 h. Blood samples were collected over 24 h post-dose, and plasma drug concentrations were determined by liquid chromatography-tandem mass spectrometry. Pharmacokinetic parameters were determined using a non-compartmental analysis, and safety was evaluated.

**Results:** Twenty-three subjects completed the study. The geometric mean ratio (90% confidence interval) of the test formulation to reference formulation was 0.9570 (0.8178 – 1.1199) for the maximum plasma concentration ( $C_{max}$ ) and 1.0720 (1.0262 – 1.1198) for the area under the concentration–time curve from dosing to the last quantifiable concentration ( $AUC_{last}$ ). The mean plasma concentration–time profiles, pharmacokinetic parameters, and safety were comparable between the two formulations.

**Conclusion:** Equivalent pharmacokinetic characteristics that satisfied the criteria of bioequivalence and similar safety profiles were observed for both test and reference formulations of voriconazole.

**Keywords:** Voriconazole; Pharmacokinetics; Bioequivalence; Safety

## INTRODUCTION

Voriconazole, a broad-spectrum antifungal agent, is a second-generation triazole with a structure similar to that of fluconazole, but with improved potency [1, 2]. It exhibits the antifungal effect primarily by inhibiting the action of fungal cytochrome P450, reducing the synthesis of ergosterol, and inhibiting the synthesis of fungal cell membrane [3, 4].

#### Author Contributions

Conceptualization: SHC. Data curation: SHC, CWK. Formal analysis: SHC. Funding acquisition: SHC, CWK, MSN. Investigation: SHC, CWK, MSN. Methodology: SHC, CWK, MSN. Project administration: SHC, MSN. Resources: SHC, CWK, MSN. Supervision: SHC, CWK, MSN. Visualization: SHC. Writing - original draft: SHC. Writing - review & editing: SHC, CWK.

Voriconazole is effective in the treatment of severe, invasive fungal infections including invasive aspergillosis and candidemia [5, 6]. It is currently marketed as 50 mg and 200 mg film-coated tablets, a 40 mg/ml powder for oral suspension, and a 200 mg powder for infusion (Vfend<sup>®</sup>, Pfizer, New York City, NY, USA).

Synthon BV (Nijmegen, Netherlands) has developed voriconazole 200 mg powder for infusion; compared with Vfend<sup>®</sup> 200 mg powder for infusion (Pfizer, USA), in this formulation, lactose is used as an additional excipient and sulfobutyl ether cyclodextrin is replaced with hydroxypropyl beta-cyclodextrin [7]. Vorico<sup>®</sup> Injection 200 mg (Chong Kun Dang Pharm., Seoul, Korea) contains the same ingredients as voriconazole 200 mg powder for infusion (Synthon BV, Nijmegen, Netherlands).

The primary objective of this randomized, open-label, single-dose, three-group, two-treatment, two-sequence, two-period, crossover, phase I clinical study was to assess the pharmacokinetic equivalence of Vorico<sup>®</sup> Injection 200 mg (test formulation) to Vfend<sup>®</sup> IV 200 mg (reference formulation). The secondary objectives were to compare the pharmacokinetic profile and safety of the test and reference formulations.

## MATERIALS AND METHODS

### 1. Subjects

The subjects eligible for this study were healthy male volunteers aged between 19 and 55 years with body weight of  $\geq 50$  kg and a body mass index (BMI) of 18.5 – 30.0 kg/m<sup>2</sup>. To eliminate the potential variability in pharmacokinetic characteristics arising due to sex, only male subjects were eligible in the study. The subjects exhibited no clinically significant abnormalities, as revealed by their medical history, vital signs, physical examination, clinical laboratory tests, and 12-lead electrocardiogram (ECG). The exclusion criteria were as follows: positive for hepatitis B surface antigen or hepatitis C or HIV antibodies at screening; 12-lead ECG with QTc >440 ms, PR <110 ms, PR >200 ms, QRS <60 ms, or QRS >110 ms at screening; and exposure to St John's Wort, rifabutin, rifampicin, carbamazepine, phenobarbital, high-dose ritonavir, terfenadine, astemizole, cisapride, pimozone, quinidine, sirolimus, ergot alkaloids (ergotamine and dihydroergotamine), or efavirenz within 1 month before the first administration of the investigational product.

### 2. Study design

This was a randomized, open-label, single-dose, three-group, two-treatment, two-sequence, two-period, crossover phase I trial (ClinicalTrials.gov identifier: NCT02631954). The study was approved by the Institutional Review Board of Inha University Hospital (IRB protocol #15-057; Incheon, Korea) and the Korean Ministry of Food and Drug Safety (MFDS). The study was conducted in accordance with the Declaration of Helsinki and Guideline for Good Clinical Practice. All subjects signed informed consent form before study enrollment.

Screening was conducted 28 to 2 days before the first dosing. For each group, eight eligible subjects were hospitalized in the inpatient clinical trial unit and were randomly assigned to one of the two sequences on the day before the first dosing and received a single dose of 200 mg test or reference formulation intravenously on day 1. The investigational products were administered at approximately 8 to 9 a.m. after an overnight fast for at least 10 h. The prepared investigational products were administered intravenously at a constant

rate of 33.3 mL/h over a 1.5-h period using an infusion pump. At the end of the infusion, approximately 12–15 mL of saline was flushed within 1 min to ensure that no investigational product remained in the intravenous administration line. The subjects were maintained under a fasting state until 4 h after the initiation of drug administration, except for water consumption 2 h after the initiation of dosing. The subjects were discharged on day 2. The washout period was 7 days; the second period was scheduled similar to the first period, except for the administration of the investigational product. An end-of-study (EOS) visit took place on days 13–20. Throughout the study period, alcohol consumption, heavy exercise, and concomitant drug (s) use were not allowed.

### 3. Investigational product preparation

To prepare 20 mL of translucent and 10 mg/mL of concentrated voriconazole solutions, 19 mL of sterile water was added to the test or reference formulation powder using an 18- or 20-G needle. Twenty milliliters of the concentrated voriconazole solution was drawn using a 50-mL syringe. Sterile saline solution (0.9% NaCl) was further drawn into the syringe to a final volume of 50 mL. The prepared solution contained 4 mg/mL voriconazole. The syringe was inverted 3–4 times to thoroughly mix the solution.

### 4. Assessments

Blood samples were collected prior to the start of infusion (SOI) (*i.e.*, pre-dose), and at 0.5, 1, 1.25, 1.5 (before the end of infusion [EOI]), 1.58, 1.67, 1.83, 2, 2.5, 3, 4, 6, 8, 12, and 24 h after the SOI for both the test and reference formulations. Plasma voriconazole concentration was detected using a validated LC-MS/MS method.

Adverse events (AEs) and the use of concomitant medication were monitored over the course of the study. Vital signs were evaluated at screening; on day -1, 1, and 2 in each period; and at the EOS visit. Clinical laboratory analyses were conducted at screening, on day -1 for each period, and at the EOS visit. A 12-lead ECG was conducted at screening and the EOS visit. A physical examination was performed at screening, on days 1 and 2 in each period, and at the EOS visit.

### 5. Endpoints

Primary pharmacokinetic endpoints were the area under the concentration-time curve (AUC) from time zero to the last quantifiable concentration ( $AUC_{last}$ ) and maximum plasma concentration ( $C_{max}$ ) of voriconazole. Secondary pharmacokinetic endpoints were the time to  $C_{max}$  ( $T_{max}$ ); AUC from time to zero to infinity ( $AUC_{inf}$ ); ratio of  $AUC_{last}$  to  $AUC_{inf}$  ( $AUC_{last/inf}$ ); terminal elimination rate constant ( $\lambda_z$ ); and terminal half-life ( $t_{1/2}$ ). Safety endpoints (*e.g.*, AEs) were also evaluated, as described above.

### 6. Statistical analysis

The sample size was calculated from a coefficient of variation of 12.3% [7] and geometric mean (GM) ratios for the primary pharmacokinetic endpoints of 1.05. A sample size of 10 was required to afford sufficient statistical power (80%) for the 90% confidence interval (CI) of the GM ratios of  $AUC_{last}$  and  $C_{max}$  to satisfy the pre-specified criteria for equivalence margin of 0.8–1.25. The sample size was determined based on two one-sided tests procedure with 0.05 level of significance for the GM ratio. Considering the dropout, the study sample size was calculated to be 24 (8 subjects per group).

All statistical analyses and pharmacokinetic analysis were conducted using SPSS® version 19.0 (IBM Corp. Armonk, NY, USA) and Phoenix WinNonlin® version 6.4 (Certara USA,

Inc., Princeton, NJ, USA). Pharmacokinetic analysis was performed in the pharmacokinetic population, which included all subjects who had received a complete dose of the study drug and provided at least one post-dose blood sample with a voriconazole concentration. Pharmacokinetic parameters were calculated using non-compartmental methods. The  $AUC_{last}$  was calculated using the linear up/log down trapezoidal method, and the  $C_{max}$  was obtained directly from the concentration–time data. The  $AUC_{inf}$  was calculated as  $AUC_{last} + C_{last}/\lambda_z$ , where  $C_{last}$  was the last observable concentration and  $\lambda_z$  was estimated at the terminal phase by linear regression after log-transformation of the concentrations. The ANOVA was performed on the natural logarithm transformed  $AUC_{last}$  and  $C_{max}$  values, and  $P < 0.05$  indicated significance. The ANOVA model considered group effect, sequence nested within group effect, period nested within group effect, treatment effect, and interaction between treatment and group effect as fixed factors. Subject within sequence-by-group interaction effect was considered a random factor. Bioequivalence was attained if 90% CIs for the GM ratios of  $AUC_{last}$  and  $C_{max}$  were within the 0.8 – 1.25 predefined equivalence boundary for the comparisons of test and reference formulation.

The safety data were analyzed in the safety population, which comprised all subjects who had been randomly assigned to a sequence and who had received either a complete or partial dose of the study drug. AEs were listed according to the organ system class and preferred terms (Medical Dictionary for Regulatory Activities [MedDRA], version 17.0) and were summarized by relationship to treatment. All safety data were evaluated descriptively.

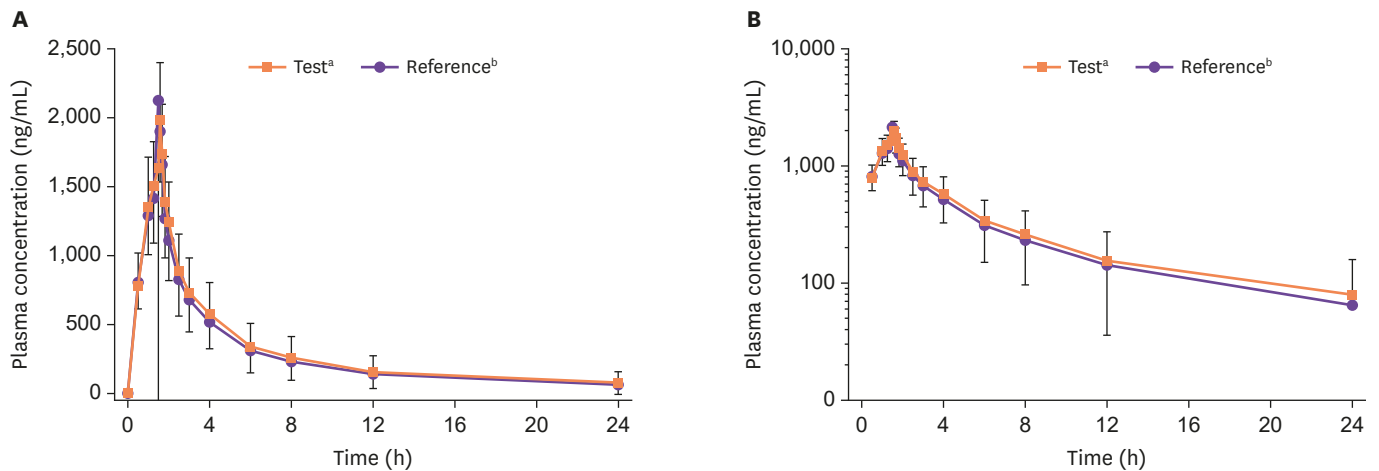
## RESULTS

### 1. Subjects

Twenty-five healthy Korean male subjects were enrolled and randomized, and one randomized subject dropped out before the administration of the study drug. The remaining 24 subjects received the study drug, and they were included in the safety population. Age, height, weight, and BMI of the safety population were  $28.0 \pm 6.7$  (mean  $\pm$  standard deviation) years,  $173.3 \pm 6.1$  cm,  $70.0 \pm 9.7$  kg, and  $23.3 \pm 2.7$  kg/m<sup>2</sup>, respectively. Among the 24 subjects who received the study drug, one subject withdrew consent before the second period. Twenty-three subjects completed the study without major deviation, and they were included in the pharmacokinetic population.

### 2. Pharmacokinetics

Pharmacokinetic parameters were determined based on the plasma voriconazole concentration data obtained from the pharmacokinetic population. Following intravenous administration of a single 200 mg dose, both test and reference formulations showed similar mean voriconazole plasma concentration–time profiles (**Fig. 1**). The pharmacokinetic parameters for voriconazole are summarized in **Table 1**. The mean (standard deviation [SD])  $AUC_{last}$  value was 7,469.78 (3,125.73) h·ng/mL for the test formulation and 6,966.17 (2,856.10) h·ng/mL for the reference formulation. The mean (SD)  $C_{max}$  value was 1,997.0 (406.2) ng/mL for the test formulation and 2,433.7 (2,456.9) ng/mL for the reference formulation. For each primary endpoint ( $AUC_{last}$  and  $C_{max}$ ), the 90% CIs of the GM ratios for the test formulation to reference formulation were all within the pre-specified margin for bioequivalence of 0.8 – 1.25 (**Table 2**). The secondary pharmacokinetic endpoints including  $T_{max}$ ,  $AUC_{inf}$ ,  $AUC_{last/inf}$ ,  $\lambda_z$ , and  $t_{1/2}$  were comparable between the two treatments.



**Figure 1.** Mean ( $\pm$  standard deviation) plasma voriconazole concentration against time, following a single intravenous dose of the reference or test formulation for 1.5 h in healthy male subjects (pharmacokinetic population): (A) linear scale, (B) semi-logarithmic scale.

<sup>a</sup>Vorico® Injection 200 mg.

<sup>b</sup>Vfend® IV 200 mg.

**Table 1.** Summary of the pharmacokinetic parameters (pharmacokinetic population)

Pharmacokinetic Parameters	Test <sup>a</sup> (n = 23)	Reference <sup>b</sup> (n = 23)
$T_{max}$ (h)		
Mean (SD)	1.58 (0.04)	1.57 (0.03)
Median (range)	1.58 (1.50 – 1.67)	1.58 (1.50 – 1.60)
$C_{max}$ (ng/mL)		
Mean (SD)	1,997.0 (406.2)	2,433.7 (2,456.9)
Median (range)	2,048.4 (1,408.2 – 3,015.6)	1,878.5 (1,323.0 – 13,571.2)
$AUC_{last}$ (h·ng/mL)		
Mean (SD)	7,469.78 (3,125.73)	6,966.17 (2,856.10)
Median (range)	6,435.36 (3,609.09 – 16,068.04)	6,166.75 (3,626.56 – 13,344.14)
$AUC_{inf}$ (h·ng/mL)		
Mean (SD)	8,631.50 (4,401.54)	8,159.24 (4,905.05)
Median (range)	7,854.27 (3,802.38 – 19,588.18)	6,458.54 (3,747.04 – 25,352.31)
$AUC_{last/inf}$		
Mean (SD)	0.90 (0.09)	0.91 (0.10)
Median (range)	0.93 (0.68 – 0.98)	0.94 (0.53 – 0.98)
$\lambda_z$ (1/h)		
Mean (SD)	0.10 (0.04)	0.10 (0.03)
Median (range)	0.10 (0.05 – 0.22)	0.10 (0.03 – 0.13)
$t_{1/2}$ (h)		
Mean (SD)	7.98 (2.92)	8.42 (4.61)
Median (range)	6.91 (3.15 – 15.22)	6.92 (5.38 – 26.82)

<sup>a</sup>Vorico® Injection 200 mg.

<sup>b</sup>Vfend® IV 200 mg.

$T_{max}$ , time to  $C_{max}$ ; SD, standard deviation;  $C_{max}$ , maximum plasma concentration;  $AUC_{last}$ , area under the concentration–time curve from time zero to the last quantifiable concentration;  $AUC_{inf}$ , area under the concentration–time curve from time zero to infinity;  $AUC_{last/inf}$ , ratio of  $AUC_{last}$  to  $AUC_{inf}$ ;  $\lambda_z$ , terminal elimination rate constant;  $t_{1/2}$ , terminal half-life.

**Table 2.** Statistical analysis of the primary pharmacokinetic endpoints (pharmacokinetic population)

Endpoints	Geometric mean		Geometric mean ratio (90% CI)
	Test <sup>a</sup> (n = 23)	Reference <sup>b</sup> (n = 23)	
$AUC_{last}$ (h·ng/mL)	6,964.44	6,496.96	1.0720 (1.0262 – 1.1198)
$C_{max}$ (ng/mL)	1,956.22	2,044.10	0.9570 (0.8178 – 1.1199)

<sup>a</sup>Vorico® Injection 200 mg.

<sup>b</sup>Vfend® IV 200 mg.

CI, confidence interval;  $AUC_{last}$ , area under the concentration–time curve from time zero to the last quantifiable concentration;  $C_{max}$ , maximum plasma concentration.

**Table 3.** Treatment-emergent adverse events according to the preferred term (safety population)

TEAEs	Test <sup>a</sup> (n = 24)	Reference <sup>b</sup> (n = 23)
Eye disorders		
Colour blindness acquired		1
Photophobia	21	18
Vision blurred		2
Visual impairment	1	1
Investigations		
Blood glucose increased	1	
Lymphocyte count decreased	1	
Urine oxalate increased	1	
White blood cells urine positive		1
Nervous system disorders		
Headache	2	
Respiratory, thoracic and mediastinal disorders		
Nasal congestion		1
Vascular disorders		
Dizziness	3	3
Epistaxis		1
<b>Total</b>	<b>30</b>	<b>28</b>

<sup>a</sup>Vorico® Injection 200 mg.

<sup>b</sup>Vfend® IV 200 mg.

TEAE, treatment-emergent adverse event.

### 3. Safety

During the study, there were no treatment-emergent AEs (TEAEs) which resulted in study discontinuation and there were no serious AEs. All TEAEs had relationship to the study drug.

Fifty-eight TEAEs were mild, and 28 cases were related to the reference formulation, where 30 cases were related to the test formulation (Table 3). All 24 (100%) subjects experienced one or more TEAEs. All subjects recovered from the TEAEs without any sequelae. Photophobia (39 cases), dizziness (6 cases), headache (2 cases), vision blurred (2 cases), and visual impairment (2 cases) were the common TEAEs. TEAEs were reported in 21 (91.3%) out of the 23 subjects who received the reference formulation and in 22 (91.7%) of the 24 subjects who received the test formulation; there was no statistically significant difference between the two formulations ( $P$ -value = 1.0; Fisher's exact test).

No treatment-related trends were founded in the results of clinical laboratory tests, vital signs, ECG, or physical examination.

## DISCUSSION

In the present study, the pharmacokinetic equivalence of a test formulation (Vorico® Injection) and a reference formulation (Vfend® IV) of voriconazole and their safety were evaluated. It has been reported that the genetic polymorphism in *CYP2C19* is a major contributing factor for the highly variable pharmacokinetics of voriconazole [8-11]. The pharmacokinetic endpoints determined in this study were comparable to those determined in clinical studies conducted in healthy male Koreans to assess the effect of *CYP2C19* polymorphism on the pharmacokinetics of voriconazole [12, 13]. After a single intravenous administration of 200 mg voriconazole in healthy Koreans, the mean (SD)  $t_{1/2}$  of extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers according to the *CYP2C19* genotype group were found to be 3.2 (2.5) h, 5.5 (3.3) h, and 13.3 (6.1) h, respectively



[13]. The mean (SD) and median (range) of the  $t_{1/2}$  obtained in our present study were 7.98 (2.92) h and 6.91 (3.15-15.22) h, respectively, for the test formulation and 8.42 (4.61) h and 6.92 (5.38-26.82) h, respectively, for the reference formulation.

The safety profiles of the test and reference formulations were comparable. No serious AEs occurred; overall, there were no unexpected safety results over the course of the study. Similar to the results of previous studies on voriconazole [13-16], a transient visual disturbance occurred shortly after dosing and it lasted a few minutes. The characteristics of eye disorders reported in this study were similar to the results of a double-blind, placebo-controlled study on the effects of multiple voriconazole doses on the vision of healthy volunteers. They which exhibited nonprogressive and reversible effects on altered visual perception, electroretinograms, color vision, and static visual field thresholds over the treatment period [17].

In this study, 24 subjects were divided into three groups in consideration of effective drug administration and safety monitoring. This group effect was considered in the ANOVA model. However, the findings of the current study have a limitation regarding the open-label design and the inclusion of only healthy male volunteers. Because the primary aim of this study was to assess the pharmacokinetic equivalence of two formulations of voriconazole, an open-label design was adopted. However, the results of the current study cannot be generalized to female or older (>55 years) patient populations owing to the limitation with regard to the study design; the study also included only male volunteers aged between 19 and 55 years.

In conclusion, this phase I trial demonstrated equivalent pharmacokinetic characteristics between Vorico® Injection 200 mg and Vfend® IV 200 mg, which satisfied the criteria of bioequivalence with respect to the primary endpoints, the  $AUC_{last}$  and  $C_{max}$  of voriconazole, after a single intravenous dose crossover administration under fasting conditions. Additionally, both formulations exhibited similar safety and tolerability.

## REFERENCES

1. Chiou CC, Groll AH, Walsh TJ. New drugs and novel targets for treatment of invasive fungal infections in patients with cancer. *Oncologist* 2000;5:120-35.  
[PUBMED](#) | [CROSSREF](#)
2. Koltin Y, Hitchcock CA. The search for new triazole antifungal agents. *Curr Opin Chem Biol* 1997;1:176-82.  
[PUBMED](#) | [CROSSREF](#)
3. Donnelly JP, De Pauw BE. Voriconazole-a new therapeutic agent with an extended spectrum of antifungal activity. *Clin Microbiol Infect* 2004;10(Suppl 1):107-17.  
[PUBMED](#) | [CROSSREF](#)
4. Sandherr M, Maschmeyer G. Pharmacology and metabolism of voriconazole and posaconazole in the treatment of invasive aspergillosis-review of the literature. *Eur J Med Res* 2011;16:139-44.  
[PUBMED](#) | [CROSSREF](#)
5. Vehreschild JJ, Böhme A, Reichert D, Kiehl MG, Arenz D, Pankraz K, Kochanek M, Ullmann AJ, Cornely OA. Treatment of invasive fungal infections in clinical practice: a multi-centre survey on customary dosing, treatment indications, efficacy and safety of voriconazole. *Int J Hematol* 2008;87:126-31.  
[PUBMED](#) | [CROSSREF](#)
6. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Segal BH, Steinbach WJ, Stevens DA, van Burik JA, Wingard JR, Patterson TF; Infectious Diseases Society of America. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46:327-60.  
[PUBMED](#) | [CROSSREF](#)
7. Medicines Evaluation Board. Medicine Information Bank. Public assessment report scientific discussion. Voriconazol Synthron 50 mg and 200 mg, film-coated tablets. Voriconazol Synthron 200 mg, powder

- for solution for infusion (voriconazole). NL/H/2709/001-003/DC. 2014. Available at: <https://www.geneesmiddeleninformatiebank.nl/Pars/h112279.pdf>. Accessed 1 March 2020.
8. Scholz I, Oberwittler H, Riedel KD, Burhenne J, Weiss J, Haefeli WE, Mikus G. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. *Br J Clin Pharmacol* 2009;68:906-15.  
[PUBMED](#) | [CROSSREF](#)
  9. Wang G, Lei HP, Li Z, Tan ZR, Guo D, Fan L, Chen Y, Hu DL, Wang D, Zhou HH. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. *Eur J Clin Pharmacol* 2009;65:281-5.  
[PUBMED](#) | [CROSSREF](#)
  10. Weiss J, Ten Hoevel MM, Burhenne J, Walter-Sack I, Hoffmann MM, Rengelshausen J, Haefeli WE, Mikus G. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. *J Clin Pharmacol* 2009;49:196-204.  
[PUBMED](#) | [CROSSREF](#)
  11. Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. *Clin Pharmacol Ther* 2004;75:587-8.  
[PUBMED](#) | [CROSSREF](#)
  12. Chung H, Lee H, Han HK, An H, Lim KS, Lee YJ, Cho JY, Yoon SH, Jang JJ, Yu KS. A pharmacokinetic comparison of two voriconazole formulations and the effect of CYP2C19 polymorphism on their pharmacokinetic profiles. *Drug Des Devel Ther* 2015;9:2609-16.  
[PUBMED](#) | [CROSSREF](#)
  13. Lee S, Kim BH, Nam WS, Yoon SH, Cho JY, Shin SG, Jang JJ, Yu KS. Effect of CYP2C19 polymorphism on the pharmacokinetics of voriconazole after single and multiple doses in healthy volunteers. *J Clin Pharmacol* 2012;52:195-203.  
[PUBMED](#) | [CROSSREF](#)
  14. Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E, Haas A, Ruhnke M, Lode H. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002;34:563-71.  
[PUBMED](#) | [CROSSREF](#)
  15. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, De Pauw B; Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;347:408-15.  
[PUBMED](#) | [CROSSREF](#)
  16. Howard A, Hoffman J, Sheth A. Clinical application of voriconazole concentrations in the treatment of invasive aspergillosis. *Ann Pharmacother* 2008;42:1859-64.  
[PUBMED](#) | [CROSSREF](#)
  17. Zrenner E, Tomaszewski K, Hamlin J, Layton G, Wood N. Effects of multiple doses of voriconazole on the vision of healthy volunteers: a double-blind, placebo-controlled study. *Ophthalmic Res* 2014;52:43-52.  
[PUBMED](#) | [CROSSREF](#)