Clinical Pharmacokinetics of Triazoles in Pediatric Patients

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Abstract
Triazoles represent an important class of antifungal drugs in the prophylaxis and treatment of invasive fungal disease in pediatric patients. Understanding the pharmacokinetics of triazoles in children is crucial to providing optimal care for this vulnerable population. While the pharmacokinetics is extensively studied in adult populations, knowledge on pharmacokinetics of triazoles in children is limited. New data are still emerging despite drugs already going off patent. This review aims to provide readers with the most current knowledge on the pharmacokinetics of the triazoles: fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole. In addition, factors that have to be taken into account to select the optimal dose are summarized and knowledge gaps are identified that require further research. We hope it will provide clinicians guidance to optimally deploy these drugs in the setting of a life-threatening disease in pediatric patients.

1 Introduction
Immunocompromised pediatric patients are at high risk for invasive fungal disease (IFD). Although advances have been made in the management of IFD, the incidence and mortality rates are still high whereas treatment options remain limited and challenging. Triazoles represent the most important class of antifungal drugs for the prophylaxis and treatment of IFD. Within this class, isavuconazole, itraconazole, posaconazole, and voriconazole are recommended for managing invasive aspergillosis [1] and fluconazole and voriconazole are recommended for managing invasive candidiasis [2, 3]. Understanding the pharmacokinetics (PK) of these triazoles in pediatric patients is crucial to provide the most beneficial treatment. While the PK of triazoles is extensively studied in adult populations, knowledge on the PK of triazoles in pediatric patients is limited. Pediatric dose recommendations of triazoles have either been adjusted several times in the past years (i.e., voriconazole) or have been reported in the literature to a limited extent (i.e., isavuconazole, itraconazole, and posaconazole). This review provides an overview of current knowledge on the PK of the triazoles fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole in pediatric populations and summarizes factors that have to be taken into account to select the optimal dose.

2 Search Methodology
Relevant articles that describe the PK of triazoles in pediatric patients were searched until 26 November, 2020 using the databases PubMed and Embase. A detailed description of the literature search strategy is given in the Electronic Supplementary Material. Conference abstracts and unpublished
Key Points

Fluconazole pharmacokinetics is extensively studied in the neonatal population but requires more extensive research in children and adolescents. Voriconazole pharmacokinetics is extensively studied in children and adolescents and could benefit from more information in the critically ill neonatal and pediatric population despite its limited clinical use in these populations.

Isavuconazole, posaconazole, and itraconazole pharmacokinetics are studied to a limited extent in pediatric populations. To our opinion, specifically isavuconazole and posaconazole pharmacokinetics need to be investigated, as these drugs are frequently used in the hematological setting.

For all triazole agents, there is very limited knowledge on pharmacokinetics in critically ill patients who are likely to have altered pharmacokinetics. In addition, information on the impact of dialysis, extracorporeal membrane oxygenation as well as renal or hepatic impairment is lacking in most cases and should warrant further exploration.

Data from conference proceedings were not included in this review.

The order of appearance of each triazole in this article is in the order of appearances of market introduction. This emphasizes the need for more prompt action to investigate the PK for the newest released drugs and to learn from pitfalls from the past. After providing a general introduction on pharmacology for all triazoles, a general introduction of each triazole will be given including indications and dose recommendations from the current labels and guidelines. Next, triazole absorption, distribution, metabolism, and elimination characteristics in adults will be described followed by relevant details on pediatric PK for both non-compartmental analyses (NCA) and population PK analyses.

3 Mechanism of Action: Pharmacology

All triazoles block the conversion of lanosterol to ergosterol through inhibition of the enzyme lanosterol 14α-demethylase (cytochrome P450 [CYP] 51). The depletion of ergosterol and accumulation of its toxic sterol precursors weaken the cell membrane structure and lead to cell membrane dysfunction [4–8]. Next to their fungal pharmacological target, triazoles are substrates and/or inhibitors of the human equivalent CYP enzyme system [4–8]. An overview of the metabolic routes and enzyme affinities of triazoles is provided in Table 1.

4 Fluconazole

The US Food and Drug Administration (FDA) approval of fluconazole in adult patients was received in 1990 and fluconazole is licensed in individual European member states since 1988 [4, 9]. Fluconazole formulations include a solution for intravenous infusion and capsules, tablets, syrup, and powder for suspension for oral administration [9]. Currently, fluconazole is approved in pediatric patients aged 0–17 years for the treatment of mucosal candidiasis, for invasive candidiasis and cryptococcal meningitis, for prophylaxis and treatment of Candida infections in immunocompromised patients, and for prophylaxis (of relapse) and treatment of cryptococcal meningitis in high-risk patients [9, 10]. The fluconazole dosing recommendations in the European and American labels, the European Society of

| Table 1 | An overview of the metabolic routes and enzyme inhibition of triazoles |
|---------|---------------------------------------------------------------|
|         | Fluconazolea   | Isavuconazole | Itraconazole | Posaconazole | Voriconazole |
| CYP2C9  | Moderate inhibitor [4, 82]                                   |                |              |             |              |
| CYP2C19 | Strong inhibitor [4, 82]                                     |                |              |             |              |
| CYP3A4/5| Moderate inhibitor [4, 82]                                   | Substrateb/strong inhibitor [6, 82] |            |              |
| UGT     | Substrateb [7]                                              |                |              |             | Substrate/inhibitorb [83] |
| P-gp    | Mild inhibitor [7]                                           |                | Inhibitorb [6, 82] |            | Substrate/inhibitorb [83] |
| CYP     | cytochrome P450, FDA US Food and Drug Administration, P-gp P-glycoprotein, UGT uridine diphosphate glucuronosyltransferase |
| aRenal excretion |
| bSubstrate sensitivity/inhibition mentioned in the FDA label and/or FDA drug interaction and labeling list, but the potency of sensitivity/inhibition is not mentioned and therefore not further specified in this table

Adis
|                   | **Europe** [10] | **FDA** [4] | **ESCMID** [2] | **IDSA** [3] |
|-------------------|-----------------|-------------|----------------|-------------|
| **Neonates**      |                 |             |                |             |
| **Preterm neonates (PNA 0–14 days)** | 3–12 mg/kg (maximum 12 mg/kg) every 72 hours | 3–12 mg/kg every 72 hours | 3–12 mg/kg every 72 hours | 3–12 mg/kg every 24 hours |
| **Preterm neonates (PNA > 14 days)** | (Loading dose 6 mg/kg, on day 1)$^a$ 3–12 mg/kg (maximum 12 mg/kg) every 72 hours |  |  |  |
| **Term neonates (PNA 0–14 days)** | 3–12 mg/kg (maximum 12 mg/kg) every 48 hours |  |  |  |
| **Term neonates (PNA 15–27 days)** | (Loading dose 6 mg/kg, on day 1)$^a$ 3–12 mg/kg (maximum 12 mg/kg) every 48 hours |  |  |  |
| **Neonates (< 1000 g)** | 3–6 mg/kg twice weekly | 3–6 mg/kg twice weekly |  |  |
| **Neonates (no PNA or GA reported)** | (Loading dose 25 mg/kg)$^a$ 12 mg/kg every 24 hours |  |  |  |
| **Infants/children/adolescents** | **Age: 28 days to 11 years** | 3–12 mg/kg (maximum 400 mg/day) every 24 hours |  |  |
| **Age: 12–18 years** | (Loading dose 6 mg/kg, maximum 400 mg, on day 1)$^a$ 3–12 mg/kg (maximum 400 mg) every 24 hours |  |  |  |
| **Infants (no age range reported)** | (Loading dose 6–12 mg/kg, maximum 800 mg, on day 1)$^a$ 3–12 mg/kg (maximum 800 mg) every 24 hours |  |  |  |
| **Age: 12–18 years** | (Loading dose 25 mg/kg)$^a$ 12 mg/kg (maximum 400 mg) every 24 hours |  |  |  |
Clinical Microbiology and Infectious Diseases (ESCMID), and the Infectious Diseases Society of America guidelines are given in Table 2. The recommendations in the labels are different from the international guidelines, but also differ slightly between these international guidelines. Consensus between labels and guidelines is necessary to provide good clinical practice.

Fluconazole is characterized by a bioavailability (F) of 90% in adults, which makes intravenous and different oral formulations interchangeable. Absorption of fluconazole is not affected by food intake. The volume of distribution (V\textsubscript{d}) of fluconazole is approximately 0.7 L/kg [4]. Fluconazole shows good penetration in a variety of body fluids and tissues, such as cerebrospinal fluid, sputum, saliva, urine, and skin [11]. The affinity of fluconazole for plasma proteins is low (10–12%). Fluconazole is minimally metabolized (~10%) and the route of elimination is primarily (~80%) unchanged via renal excretion. Mean clearance (CL) of fluconazole is around 0.0138 L/h/kg in adults [4].

4.1 Non-Compartmental Analysis of Fluconazole PK in Pediatric Patients

Six studies described NCA of fluconazole PK in pediatric patients [12–17]. One study was performed in neonates [12] and five studies were performed in infants and children [13–17]. A detailed overview of the dosing regimens and fluconazole pharmacokinetic results is given in Table 3. The neonatal study included 12 premature neonates aged <24 h after birth receiving fluconazole intravenously in a dose of 6 mg/kg with a dose interval of 72 h [12]. The five studies in preterm and term infants and children included patients with hematological or non-hematological malignancies, congenital disease, neoplastic disease, human immunodeficiency virus (HIV), or patients with and without peritoneal dialysis (PD) after open heart surgery with an age range of 2 weeks to 16 years [13–17]. Doses of fluconazole were 2–8 mg/kg per day administered either intravenously or as an oral suspension [13–17].

Although three out of these six studies included fluconazole as an oral formulation, none of them described the relative or absolute F of fluconazole [13, 15, 16]. During the first 2 weeks after birth, the V\textsubscript{d} of fluconazole in premature neonates almost doubled and CL increased more than two times [12]. After 2 weeks of life, the V\textsubscript{d} of premature neonates was found to be higher compared with children [12, 14, 15, 17]. After this period, the V\textsubscript{d} decreased [14, 15, 17] and comparable values to adults were reported in children aged ≥12 years. [4, 15] These data suggest that premature neonates aged ≥2 weeks need adequate loading doses compared to premature neonates straight after birth and that children aged <12 years need adequate loading doses compared to older children and adults. The higher V\textsubscript{d}
of fluconazole in premature neonates vs children and adults might be explained by the characteristics of fluconazole and body composition of neonates. Fluconazole is a hydrophilic compound, and neonates tend to have a higher water:fat ratio and as such a higher \( V_d \) [18]. The increasing fluconazole CL observed in neonates during the first 2 weeks of life might be explained by the maturation of the kidney function during this period [19]. Clearance of fluconazole in premature neonates seemed to reach the same range as children 2 weeks after birth [14, 17] but was still higher compared with adults [4]. A higher maintenance dose or shorter dosing intervals might be needed in premature neonates, infants, and children compared with adults. Contrary to these studies, one study in premature infants aged <3 months reported comparable CL to adults, after a single dose of fluconazole [15]. Three studies described exposure of fluconazole after different dosing regimens and found a dose-proportional increase in exposure [15–17]. In patients with PD, no statistical differences in \( V_d \) and CL were reported compared to non-PD children with mild renal dysfunction. However, the elimination half-life of fluconazole was significantly longer in PD patients. This points towards the need for a lower maintenance dose or a longer dosing interval in this pediatric PD population [14]. To our knowledge, no other disease variables, such as HIV, have been found to alter the exposure of fluconazole [15–17].

### 4.2 Population Pharmacokinetic Analysis of Fluconazole in Pediatric Patients

Nine population pharmacokinetic studies were conducted that included either neonatal patients [20, 21], a mixed patient population of neonates and infants [22–27], or children and adolescents aged 3 days to 15.9 years [28]. One of these studies pooled data from three previously reported studies [26]. A detailed overview of the dosing regimens and fluconazole pharmacokinetic results is given in Table 4. The following patient groups were included in these studies: preterm and term patients at risk for IFD, patients with suspected or documented oral or invasive *Candida* infections, patients supported with extracorporeal membrane oxygenation (ECMO), or immunocompromised hematopoietic patients. Eight studies described fluconazole PK in a one-compartment model [20–27], of which two studies included first-order absorption in the pharmacokinetic model [20, 21]. One study described fluconazole data best with a two-compartment model and first-order absorption [28]. The pharmacokinetic models and tested covariates are summarized in Table 5.

Overall, population pharmacokinetic studies showed that the relative \( F \) from 90.9 to 100% [20, 21, 28] in neonates, infants, and children was excellent, and was comparable to a \( F \) of >90% in adults [4]. The rate of oral bioavailability (\( K_a \)) was from 0.538 to 3.76 h \(^{-1} \) [20, 21, 28]. It is difficult to compare values of \( V_d \) and CL between fluconazole population pharmacokinetic studies directly, as a variety of covariates were included on \( V_d \) and CL. Allometrically scaled bodyweight with fixed [20, 21, 23] and/or estimated [20] exponents was added on either \( V_d \) [20, 21, 23] and/or CL [20, 21, 23]. Age (inversely related) [27], ECMO [25], a coefficient for ECMO [26] and/or linearly scaled bodyweight [26, 28] were included as covariates on \( V_d \). Covariates as linearly scaled bodyweight [26], body surface area [28], serum creatinine [24, 25], and exponents for estimated glomerular filtration (estimated) [20], serum creatinine [21, 23, 26], postmenstrual age (PMA) as a function of gestational age (GA) and postnatal age (PNA), [21] gestational age at birth (BGA) [23] and/or PNA [23], were included on CL. Serum creatinine was inversely related to CL [21, 23–26]. In one study, it was not clear if postmenstrual age was included as a covariate on fluconazole CL in the final model [22]. Another study reported that bodyweight influenced fluconazole CL but did not report the covariate equation [22]. Three studies used a linear regression analysis to test covariates [24, 25, 28]. One study concluded that fluconazole CL in premature neonates was low at birth and doubled within the first month after birth, but did not report on changes in fluconazole \( V_d \) [23]. This conclusion is slightly different from a previous NCA report, which reported a more than two-fold increase in CL during the first 2 weeks of life. Another study included both ECMO and non-ECMO patients and reported a significantly higher \( V_d \) but similar CL in pediatric ECMO patients compared with non-ECMO patients [26]. This higher \( V_d \) is likely due to the hydrophilic nature of fluconazole and the large circulating volume of ECMO procedures [29]. These population pharmacokinetic results point toward the need for an adequate loading dose of fluconazole in pediatric ECMO patients.

### 4.3 Physiologically Based PK of Fluconazole

Two studies have obtained interesting pharmacokinetic information with physiologically based pharmacokinetic models and assessed fluconazole dosing by predicting either cerebrospinal fluid exposure or the influence of ECMO [30, 31]. Data from plasma samples of 166 infants (<750 g) with a median PNA of 21 days (range 3–93 days) and cerebrospinal fluid samples of 22 infants with a median PNA of 28 days (range 24–33 days) showed fluconazole exposure in the central nervous system, with a central nervous system-to-plasma ratio of ~1 [30]. In the second study, the edema disease state of ECMO patients was added to the model and the authors suggested that edema contributes to lower fluconazole exposure [31].
Table 3  Non-compartmental analyses of fluconazole

| Population | Dose | Formulation | Weight | N | SD, FD, or MD | Pharmacokinetic parameters | References |
|------------|------|-------------|--------|---|---------------|-----------------------------|------------|
|            |      |             |        |   |               | $C_{\text{max}}$ | $C_{\text{min}}$ | $T_{\text{max}}$ | $AUC$ | $T_{1/2}$ | $\text{CL}$ | $V_1$ |
| Premature neonates aged < 24 h after birth | 6 mg/kg IV with a dose interval of 72 h | IV | NR | 12 | FD | day 1 | Mean (range)$^a$ | 5.5 mg/L (3.7–10.2) | NR | Mean (range) | 2.2 h (0.2–6.6) | Mean (range)$^b$ | 88.6 h (43.3–187.3) | Mean (range)$^b$ | 0.011 L/h/kg (0.005–0.017) | Mean (range) | 1.18 L/kg (1.05–1.48) |
|          |      |             |        |   | MD | day 7 | Mean (range)$^a$ | 12.8 mg/L (6.0–17.8) | NR | Mean (range) | 1.6 h (0.25–6.3) | Mean (range)$^a$ | 67.5 h (30.8–130.8) | Mean (range)$^b$ | 0.020 L/h/kg (0.009–0.045) | Mean (range) | 1.84 L/kg (0.30–5.71) |
|          |      |             |        |   | MD | day 13 | Mean (range)$^a$ | 10.0 mg/L (6.0–14.1) | NR | Mean (range) | 1.6 h (0.25–6.7) | Mean (range)$^a$ | 55.2 h (31.2–70.7) | Mean (range)$^b$ | 0.031 L/h/kg (0.016–0.046) | Mean (range) | 2.25 L/kg (1.49–3.68) |
| Premature infants < 3 months of age | 6 mg/kg daily | IV (N = 2) and PO (N = 6) [suspension] | NR | 6 | SD | Median (range)$^a$ | 9.6 mg/L (6.0–13.5) | NR | NR | Median (range)$^a$ | 412 mg*h/L (340–636) | AUC$_{\text{inf}}$ | NR | Median (range)$^a$ | 0.014 L/h/kg (0.007–0.017) | NR | [13] |
| Children with or without PD after open heart surgery aged 2 weeks to 3 years | 3 mg/kg daily | IV | Mean (STDV) | 4.0 kg (1.1) | MD | PD | Mean (STDV) | 2.13 mg/L (0.99) | C$_{\text{max}}$ day 1 | 3.86 mg/L (2.86) | C$_{\text{max}}$ day 2 | 5.32 mg/L (4.06) | C$_{\text{max}}$ day 3 | 4.60 mg/L (3.43) | C$_{\text{max}}$ day 4 | 1.66 mg/L (0.88) | C$_{\text{max}}$ day 1 | 2.23 mg/L (1.22) | C$_{\text{max}}$ day 2 | 3.17 mg/L (1.64) | C$_{\text{max}}$ day 3 | 2.60 mg/L (1.12) | C$_{\text{max}}$ day 4 | 1.66 mg/L (0.88) | 2.23 mg/L (1.22) | 3.17 mg/L (1.64) | 2.60 mg/L (1.12) | 1.66 mg/L (0.88) | 2.23 mg/L (1.22) | 3.17 mg/L (1.64) | 2.60 mg/L (1.12) | Mean (STDV)$^a$ | 72.4 h (9.7) | Mean (STDV)$^a$ | 0.018 L/h/kg (0.008) | $\text{CL}_{\text{ef,frac}}$ | 0.014 L/h/kg (0.005) | $\text{CL}_{\text{plasma}}$ (24 h peritoneal clearance) | 1.39 L/kg (0.22) |
|          |      |             |        | 17 | MD | Non-PD | Mean (STDV) | 2.84 mg/L (0.83) | C$_{\text{max}}$ day 1 | 5.43 mg/L (2.17) | C$_{\text{max}}$ day 2 | 6.93 mg/L (3.89) | C$_{\text{max}}$ day 3 | 6.23 mg/L (1.97) | C$_{\text{max}}$ day 4 | 2.03 mg/L (1.14) | C$_{\text{max}}$ day 1 | 3.06 mg/L (1.32) | C$_{\text{max}}$ day 2 | 4.00 mg/L (2.35) | C$_{\text{max}}$ day 3 | 4.15 mg/L (0.95) | C$_{\text{max}}$ day 4 | 2.03 mg/L (1.14) | 3.06 mg/L (1.32) | 4.00 mg/L (2.35) | 4.15 mg/L (0.95) | 2.03 mg/L (1.14) | 3.06 mg/L (1.32) | 4.00 mg/L (2.35) | 4.15 mg/L (0.95) | Mean (STDV)$^a$ | 30.9 h (4.0) | Mean (STDV)$^a$ | 0.025 L/h/kg (0.043) | $\text{CL}_{\text{ef,frac}}$ | 0.014 L/h/kg (0.0032) | $\text{CL}_{\text{renal}}$ (24 h) | 1.07 L/kg (0.11) |
| Population                              | Dose                        | Formulation | Weight | N   | Pharmacokinetic parameters | References |
|-----------------------------------------|-----------------------------|-------------|--------|-----|-----------------------------|------------|
| Immunocompromised children              | 2, 3, or 8 mg/kg daily      | IV and PO   | NR     | 101 | \( C_{\text{max}} \) | [15]       |
| (congenital disease, HIV, malignant     |                             |             |        |     | \( C_{\text{min}} \)     |            |
| disease or prematurity) aged 0.25–16     |                             |             |        |     | \( T_{\text{max}} \)     |            |
| years                                   |                             |             |        |     | AUC                          |            |
|                                         |                             |             |        |     | Mean (STDV)\(^a\)           |            |
|                                         |                             |             |        |     | \( T_{1/2} \)              |            |
|                                         |                             |             |        |     | CL                           |            |
|                                         |                             |             |        |     | \( V_{d} \)                |            |

\(^a\) Mean (STDV) = mean (standard deviation).

\(^b\) AUC<sub>inf</sub> = AUC to infinity.
| Population                                      | Dose               | Formulation | Weight | N     | SD, FD, or MD | Pharmacokinetic parameters | References |
|------------------------------------------------|--------------------|-------------|--------|-------|---------------|----------------------------|------------|
| Children with HIV aged 5–13 years               | 2 or 8 mg/kg PO (suspension) | NR          | 9      |       | SD            | Median (range)              |            |
|                                                 |                    |             |        |       | 2 mg/kg       | 2.95 mg/L (2.31–4.40)       |            |
|                                                 |                    |             |        |       | 8 mg/kg       | 10.3 mg/L (5.44–12.14)      |            |
|                                                 |                    |             |        |       | 2 mg/kg       | 2 mg/kg                      |            |
|                                                 |                    |             |        |       | 8 mg/kg       | 8 mg/kg                      |            |
| Children with neoplastic disease aged 5–15 years| 2, 4, or 8 mg/kg IV daily for 7 days | IV          | 24     |       | Mean (range)  | Mean (SEM)                 |            |
|                                                 |                    |             |        |       | 35.6 kg (16–60) | 3.9 mg/L (0.20)             |            |
|                                                 |                    |             |        |       | 36.6 kg (25–64) | 6.4 mg/L (0.31)             |            |
|                                                 |                    |             |        |       | 35.5 kg (18–55) | 9.5 mg/L (0.14)             |            |
|                                                 |                    |             |        |       | Mean (range)  | Mean (SEM)                 |            |
|                                                 |                    |             |        |       | 36.9 kg (16–60) | 5.4 mg/L (0.39)             |            |
|                                                 |                    |             |        |       | 36.8 kg (25–64) | 10.5 mg/L (0.69)            |            |
|                                                 |                    |             |        |       | 38.6 kg (30–55) | 14.3 mg/L (0.35)            |            |
|                                                 |                    |             |        |       | Mean (range)  | Mean (SEM)                 |            |
|                                                 |                    |             |        |       | 36.9 kg (16–60) | 2.5 mg/L (0.30)             |            |
|                                                 |                    |             |        |       | 36.8 kg (25–64) | 3.2 mg/L (0.55)             |            |
|                                                 |                    |             |        |       | 38.6 kg (30–55) | 5.5 mg/L (0.29)             |            |
|                                                 |                    |             |        |       | 26 Overall    | Mean (SEM)                 |            |
|                                                 |                    |             |        |       | NR            | 17.4 h (1.1)                 |            |

\( AUC \) area under the curve, \( CL \) clearance, \( C_{max} \) maximal serum concentration, \( C_{min} \) minimal serum concentration, \( C_{trough} \) trough concentration, \( F \) bioavailability, \( FD \) first dose, \( h \) hours, \( HIV \) human immunodeficiency virus infection, \( IV \) intravenous, \( MD \) multiple dose, \( N \) total patients, \( NR \) not reported, \( PD \) peritoneal dialysis, \( PO \) 'per os', \( SD \) single dose, \( SEM \) standard error of the mean, \( STDV \) standard deviation, \( t_{1/2} \) elimination half-life, \( T_{max} \) time to reach \( C_{max} \), \( V_d \) volume of distribution

*Values recalculated/adjusted from the original paper to create uniformity of units (when individual values were reported, the median was calculated from these values)

Data only available from one patient

The study of Brammer et al. pooled data of 113 patients from previous studies. The 12 patients of the study of Saxen et al. were only reported and not analyzed in this pooled study and therefore not mentioned here (\( N = 101 \)). The study of Lee et al. was also included in this pooled study but the results of the 4-mg/kg regimen are not reported
Table 4  Population pharmacokinetic estimates of fluconazole

| Population | Dose | Formulation | Weight | N  | SD, FD, or MD | Pharmacokinetic parameters | References |
|------------|------|-------------|--------|----|---------------|-----------------------------|------------|
|            |      |             |        |    |               | AUC | $T_{1/2}$ | CL  | $V_1$ | $Q$ | $V_2$ | $K_a$ | $F$ |          |
| Preterm neonates at risk for invasive candidiasis with a median PNA of 3 days | 3 mg/kg with a dose interval of 72 h | IV and PO (orogastric tube) | Median (range) | 1.1 kg (0.9–1.3) | 75 | MD | NR | NR | 0.0197 $\times$ (WT/1.00)$^{0.746}$ $\times$ (eGFR/25.0)$^{0.463}$ | 1.04 $\times$ (WT/1.00)$^a$ | NR | NR | Estimate (RSE%) 0.538 1/h (18.5) | Estimate (RSE%) 0.909 (7.03) | [20] |
| Preterm neonates < 750 g with a median PNA of 23 days | 6 mg/kg twice weekly | IV and PO (suspension) | Median (range) | 0.71 kg (0.35–2.7) | 141 | MD | NR | NR | 0.0127 $\times$ (SCR/0.8)$^{0.41}$ $\times$ (PMA/28)$^{2.05b}$ | 1.00$^b$ | NR | NR | Point estimate (SEE) 0.96 1/h (0.25) | Point estimate (SEE) 1.00 (0.065) | [21] |
| Preterm and term neonates and infants with suspected or proven candidiasis and a 23- to 40-week gestation and a mean PNA of 13.5 days | <30 weeks CGA: loading dose 25 mg/kg, maintenance dose 12 mg/kg | IV | Median (range) | 1.26 kg (0.750–4.255) | 18 | MD | Median (95% CI) 490.9 mg*h/L (406.2–571.9) AUC$_{0-24}$, day 1 898.2 mg*h/L (503.4–1445.7) AUC$_{0-24}$ SS | Median (95% CI) 16.2–78.4 | Median (95% CI) 0.015 L/h/kg (0.008–0.039) | Median (95% CI) 0.913 L/kg (0.913–0.913) | NR | NR | NR | NR | [22] |
|            | ≥30 weeks CGA: loading dose 25 mg/kg, maintenance dose 20 mg/kg | | | | | | | | | | | | | |
| Population                                     | Dose | Formulation | Weight | N  | SD, FD, or MD | Pharmacokinetic parameters | References |
|------------------------------------------------|------|-------------|--------|----|---------------|-----------------------------|-------------|
|                                              |      |             |        |    |               | AUC | T_{1/2} | CL | V | Q | V2 | K_{a} | F |             |
| Neonates and infants with oral candidiasis or at risk for invasive fungal disease aged between 9 days and 4.4 months | 3 mg/kg | IV         | Mean (SEM) 4.1 kg (0.2) | 14 | SD | Mean (SEM) 90.2 mg*h/L (9.0) | Mean (STDV) 22.5 h (2.2) | Mean (SEM) 0.0378 L/h/kg (0.0056) | Mean (SEM) 1.17 L/kg (0.14) | NR | NR | NR | NR | [27] |
| Preterm and term infants at risk for invasive candidiasis with a 23- to 42-week gestation and aged < 120 days | Dosing range 3–12 mg/kg/dose | IV | Median (range) 1.020 kg (0.451–7.125) | 55 | MD | NR | 0.015 × (WT/1.00)^{0.75} × (BGA/26)^{1.779} × (PNA/2)^{1.227} × (SCR/1)^{-4.856}/CRAF | 1.024 × (WT/1.00)^{1} | NR | NR | NR | NR | [23] |
| Population                                      | Dose                                                                 | Formulation | Weight | N  | SD, FD, or MD | Pharmacokinetic parameters | References |
|-------------------------------------------------|----------------------------------------------------------------------|-------------|--------|----|---------------|-----------------------------|------------|
| Hospitalized neonates and infants at risk for invasive fungal disease and a median gestation age of 37 weeks aged < 60 days | Loading dose (25 mg/kg IV), followed by maintenance therapy (12 mg/kg daily) | IV          | NR     | 8  | MD            | AUC  | $T_{1/2}$  | CL    | $V_1$ | $Q$ | $V_2$ | $K_a$ | $F$ |         | [24] |
|                                                  |                                                                      | IV          | Median (IQR) | 479 | (347–496) AUC$_{0-24}$ | 56 h (26–80) | 0.016 L/h/kg (0.013–0.021) | Median (IQR) | 1.051 L/kg (0.858–1.461) | NR | NR | NR |
| Infants supported with ECMO, with a 23- to 41-week gestation and aged < 120 days | IV prophylaxis: 25 mg/kg once a week Followed by IV treatment: 12 mg/kg daily in patients with suspected or known fungal disease | IV          | Median (IQR) | 3.2 kg (2.6–3.4) | 322 | (307–343) AUC$_{0-24}$ | 60 h (47–76) | 0.017 L/h/kg (0.014–0.022) | Median (IQR) | 1.5 L/kg (1.3–1.7) | NR | NR | NR | [25] |
Table 4 (continued)

| Population Dose Formula- | Weight | N | Pharmacokinetic parameters | References |
|--------------------------|--------|---|-----------------------------|------------|
| AUC                      | \( T_{1/2} \) | CL | \( V_1 \) | \( Q \) | \( V_2 \) | \( K_a \) | \( F \) |
| IV and PO (tablets)      | Mean (STDV) | 0.019 \times WT \times (SCR/0.4)^{-0.29} | 0.93 \times WT \times 1.4^{ECMO} | NR | NR | NR | NR | [26] |
| SD and MD                | Mean (STDV) | 0.0380 L/h/kg | Mean (STDV)c | Mean (STDV) | NR | NR | Mean (STDV) | Mean (STDV) | [28] |
| IV                       | Mean (range) | 40 (21 with ECMO) | 0.562 L/kg | 3.76 1/h | 0.92 (0.09) | [28] |
| SD and MD                | Mean (STDV) | 15.63 h | 0.112 | 0.106 | 3.21 (3.21) | 4.88 (4.88) |
| IV                       | Mean (range) | 3.4 kg | 0.0380 L/h/kg | Mean (STDV) | 0.562 L/kg | 3.76 1/h | 0.92 (0.09) |
| SD and MD                | Mean (STDV) | 0.0380 L/h/kg | Mean (STDV)c | Mean (STDV) | NR | NR | Mean (STDV) | Mean (STDV) | [28] |
| IV                       | Mean (range) | 3.4 kg | 0.0380 L/h/kg | Mean (STDV) | 0.562 L/kg | 3.76 1/h | 0.92 (0.09) |
| SD and MD                | Mean (STDV) | 15.63 h | 0.112 | 0.106 | 3.21 (3.21) | 4.88 (4.88) |

AUC area under the curve, CGA corrected gestational age, CI confidence interval, CL clearance, ECMO extracorporeal membrane oxygenation, F bioavailability, FD first dose, h hours, IV intravenous, \( K_a \) rate of oral bioavailability, MD multiple dose, N total patients, NR not reported, PNA postnatal age, PO ‘per os’ (oral administration), Q intercompartmental clearance, RSE relative standard error, SCR serum creatinine, SD single dose, SEE standard error of estimate, \( t_{1/2} \) elimination half-life, \( V_1 \) volume of distribution in the central compartment, \( V_2 \) volume of distribution of the peripheral compartment, \( V_d \) volume of distribution, \( V_{d,SS} \) volume of distribution at steady state, WT weight

*Fixed or estimated value of exponent used for allometric scaling of volume of distribution was not reported

*Unclear how WT was standardized in this equation

*Values recalculated/adjusted from original paper to create uniformity of units

*WT normalized to 1 kg/week (1 week) and CR (creatinine value) = 1 if SCRT > 1 mg/dL, CR = 0 if SCRT ≤ 1 mg/dL

*ECMO = 1 or 0

*Only one patient received fluconazole treatment

*Number of ECMO patients reported in this pooled study does not add up with the number of ECMO patients in the individual studies
| Population | Subjects, N | Samples, N | Program | Covariates tested | Compartments | PO/IV | Covariates in final model | References |
|------------|-------------|------------|---------|-------------------|--------------|-------|--------------------------|------------|
| Preterm neonates at risk for invasive candidiasis with a median PNA of 3 days | 75 | 303 | NONMEM | WT, HT, eGFR, SCR, GA, PMA, PNA, ALT, AST, BUN | 1, with first-order absorption | IV and PO | eGFR with estimated exponent, allometrically scaled WT with estimated exponent. Both normalized to a standard individual | [20] |
| Preterm neonates < 750 g at risk for invasive candidiasis with a median PNA of 23 days | 141 | 604 | NONMEM | WT, PNA, GA, PMA, SCR, ALB, race, ethnicity, intubation status, mode of delivery (Cesarean section or vaginal) | 1, with first-order absorption | IV and PO | Allometrically scaled WT with a fixed exponent of 0.75, SCR, PMA (as function of GA and PNA). All normalized to a standard individual | [21] |
| Preterm and term neonates and infants with suspected or proven candidiasis and a 23- to 40-week gestation and a mean PNA range 13.5 days | 18 | 82 | NONMEM | WT, PMA | 1 | IV | WT<sup>a</sup> | [22] |
| Neonates and infants with oral candidiasis or at risk for invasive fungal disease aged between 9 days and 4.4 months | 14 | NR | TOPFIT | Age | 1 | IV | Age | [27] |
| Population | Subjects, N | Samples, N | Program | Covariates tested | Compartments | PO/IV | Covariates in final model | References |
|------------|------------|------------|---------|------------------|--------------|-------|--------------------------|------------|
| Preterm and term infants at risk for invasive candidiasis with a 23- to 42-week gestation and aged < 120 days | 55 | 357 | NONMEM | WT, BGA, PNA, PMA (defined as BGA plus PNA in weeks), and SCR | 1 | IV | Allometrically scaled WT with a fixed exponent of 0.75, BGA, PNA, and SCR. All normalized to a standard individual | [23] |
| Hospitalized neonates and infants at risk for invasive fungal disease and a median gestation age of 37 weeks aged < 60 days | 8 | 57 | WinNonLin | SCR (linear regression analysis) | 1 | IV | SCR | NR | NR | NR | NR | [24] |
| Infants supported with ECMO, with a 23- to 41-week gestation and aged < 120 days | 10 | 62 First dose 47 Multiple dose | WinNonLin | SCR, ECMO (linear regression analysis) | 1 | IV | SCR | ECMO | NR | NR | NR | NR | [25] |
| See reference [23–25]. From study [24] only patients with a GA of ≥ 36 weeks were included | 40 of which 21 with ECMO | 360 | NONMEM | WT, ECMO support, volume of blood required to prime the ECMO circuit, ratio of blood prime volume to the estimated native blood volume of the child, hemofiltration, use of CVVHD, SCR, ALB, AST, ALT, PNA, sex, race | 1 | IV | Exponent for creatinine, WT | Coefficient for ECMO, WT | NR | NR | NR | NR | [26] |
4.4 Summary of Findings and Recommendations

Pharmacokinetic data of fluconazole in neonates and infants are abundant, and pharmacokinetic data of fluconazole in children and adolescents are scarce. Research topics should include the $F$ of all different oral fluconazole formulations and full pharmacokinetic investigations in children and adolescents. Special patient populations such as critically ill pediatric patients with renal impairment or other renal replacement therapy and solid organ transplant recipients should be further investigated. Additionally, the influence of the disease state of patients, such as excess fluid retention, on fluconazole PK might be interesting to further explore.

The relative $F$ of fluconazole in pediatric patients is comparable to the $F$ described in adults, which suggests that different formulations of fluconazole are interchangeable in pediatric patients. Most of these studies included the suspension as oral formulation, data on $F$ of other oral formulations are very limited in pediatric patients.

Non-compartmental analyses report a higher $V_d$ in preterm neonates compared with children and adults. These results suggest that adequate loading doses are needed. In preterm neonates, the fluconazole CL increases during the first 2 weeks after birth. The CL after 2 weeks of birth is comparable to CL in children but higher as compared to CL in adults. These results imply that higher maintenance doses or shorter dosing intervals are needed in preterm neonates and children. Non-compartmental analyses in pediatric PD patients report a significantly increased elimination half-life for fluconazole and these data suggest a lower maintenance dose or a longer dosing interval in this pediatric population.

Population PK studies report that allometrically scaled bodyweight and ECMO are significant covariates on $V_d$. As a consequence, pediatric patients receiving ECMO might need higher loading doses. Allometrically scaled bodyweight, serum creatinine (inversely related), and either PMA (as a function of GA and PNA), or GA and PNA are significant covariates on CL. Dose adjustments based on serum creatinine, GA, and PNA might be taken into account to optimize fluconazole use. A standardized method to report both allometric scaling and maturation would be useful to compare pharmacokinetic results from different studies and populations.

Dose recommendations for fluconazole are inconsistent between the labels and the ESCMID and Infectious Diseases Society of America guidelines. As outlined previously by others [22], agreement between labels and international guidelines is necessary for clinical practice. Currently, there is no possibility to translate expert consensus from guidelines to an updated product information sheet. A reference in the summary of product characteristics to relevant guidelines would be an option to cover this. However, the legal background to make it possible for authorities and the
pharmaceutical industry to request and update their product information will be tremendously challenging.

5 Itraconazole

Itraconazole was approved for adult patients in 1992 by the FDA [6] and itraconazole has been licensed in individual European member states. The oral capsules and oral solution are widely available in contrast to the intravenous formulations [32]. Itraconazole is not approved in pediatric patients aged < 18 years [6, 33]. However, the pediatric ESCMID-ECMM guideline for invasive aspergillosis and the pediatric ESCMID guideline for invasive candidiasis recommend a dose of 2.5 mg/kg twice daily of the oral solution for the purpose of mold and yeast active prophylaxis in children aged 2–18 years [1, 2]. For treatment of a proven or probable invasive aspergillosis, itraconazole is recommended in a loading dose of 5 mg/kg twice daily of the oral solution on day 1, followed by 2.5 mg/kg twice daily in patients aged 2–18 years [1].

In adults, itraconazole has a variable F with an absolute oral F of the oral solution of 55% [6]. The F of the oral solution is ~30% higher compared with the oral capsules [34]. Because of the variable F between formulations, these are not interchangeable. Food intake and pH fluctuation influence the itraconazole uptake, therefore the oral capsules are advised to be administered in a fed state and the oral solution in a fasted state [35]. The Vd of itraconazole is > 700 L [6]. Itraconazole penetrates into a variety of body tissues, including the lung, kidney, liver, bone, stomach, spleen, muscle, keratinous tissue, and skin but does not penetrate well into the cerebrospinal fluid [36–38]. Itraconazole has an active metabolite hydroxy-itraconazole with comparable in vitro activity to the parent compound. Both itraconazole (99.8%) and hydroxy-itraconazole (99.6%) are highly bound to plasma proteins. Itraconazole is mainly metabolized via CYP3A4 (Table 1). Renal elimination of both itraconazole and hydroxy-itraconazole is < 1%. The inactive metabolites of itraconazole are excreted in the urine (35%) and feces (54%). Mean CL of itraconazole in adults is 16.68 L/h [6].

5.1 Non-Compartmental Analysis of Itraconazole PK in Pediatric Patients

To our knowledge, there are no NCA reports of itraconazole PK described in neonates. Six studies performed NCA of itraconazole in infants, children, and adolescents aged 0.5–17 years at risk of mucosal fungal infection or IFD. A detailed overview of the dosing regimens and itraconazole pharmacokinetic results is given in Table 6. Patients with hematological and non-hematological malignancies, liver transplantation, respiratory tract infections, HIV, cystic fibrosis (CF), other infections/diseases, or undergoing hematopoietic stem cell transplantation (HSCT) were included in these studies. Itraconazole was administered in different oral and intravenous dosing regimens for prophylaxis and/or treatment. Dosages of itraconazole were from 2.5 to 5 mg/kg once or twice daily, with or without a loading dose of 5 mg/kg twice daily [39–44].

In five studies, itraconazole was administered as an oral solution [40–44], of which one study also included the intravenous formulation but the authors did not report the F of itraconazole [40]. Three studies stratified pharmacokinetic results of itraconazole by age [39, 42, 43]. A single dose of 2.5 mg/kg or multiple dosing regimens of 5 mg/kg once daily or 2.5 mg/kg twice daily have been investigated in patients aged 0.5–2 years, 2–5 years, and/or > 5 years [39, 42, 43]. Exposures differ widely between groups and studies. Both CL and Vd appear to change strongly within these groups. Interestingly, administration of a 2.5-mg/kg twice-daily regimen resulted in much higher itraconazole and hydroxy-itraconazole exposures compared with a 5-mg/kg once-daily regimen of itraconazole [42–44]. This is possibly owing to saturable absorption. One study in patients undergoing HSCT reported a considerably higher exposure compared with other studies, which is most likely explained by including a loading dose for itraconazole (5 mg/kg twice daily on day 1, followed by 5 mg/kg once daily) and pharmacokinetic sampling after the third administered dose [40]. Special pediatric populations, such as patients with HIV, showed comparable exposures of itraconazole and hydroxy-itraconazole to other populations, while patients with CF showed a considerably lower exposure after 2.5 mg/kg of itraconazole twice daily compared with other pediatric populations [41, 44]. Higher dosages than 2.5 mg/kg twice daily might be needed in pediatric patients with CF.

5.2 Population Pharmacokinetic Analysis of Itraconazole in Pediatric Patients

Two population pharmacokinetic studies in pediatric patients have been published [39, 45]. A detailed description of the dosing regimens and itraconazole pharmacokinetic results is given in Table 7. The pharmacokinetic models and covariates tested are summarized in Table 8.

In 33 patients at risk for IFD aged 0.5–17 years, itraconazole was given intravenously as a single 2.5-mg/kg dose. Underlying diseases included CF, malignancies with febrile neutropenia, respiratory tract infections, or other diseases/infections. A three-compartment model best fitted the data for itraconazole. All parameter estimates were scaled to a total body weight of 30 kg [39], but the covariate equations were not reported.

In 49 patients with CF and undergoing bone marrow transplantation aged 0.4–30 years, including five adult
### Table 6 Non-compartmental analyses of itraconazole

| Population | Dose | Formulation | Weight | N | Pharmacokinetic parameters | References |
|------------|------|-------------|--------|---|-----------------------------|------------|
|            |      |             |        |   | $C_{\text{max}}$ | $C$ | $T_{\text{max}}$ | AUC | $T_{1/2}$ | CL | $V_d$ |
| Children at risk for IFD aged 0.5–17 years | 2.5 mg/kg | IV | Mean (STDV) 31.1 kg (22.7) | 33 | SD | $0.827 \text{ mg}\cdot\text{h}/\text{L}$ | NR | NR | ITZ\textsuperscript{a} | ITZ | ITZ\textsuperscript{a} | ITZ\textsuperscript{a} | [39] |
| > 0.5–2 years | > 2–6 years | > 6–12 years | > 12–16 years | Overall | ITZ\textsuperscript{a} | Mean (STDV) 0.827 mg\cdot h/L (0.859) | 0.785 mg\cdot L (0.301) | 0.806 mg\cdot L (0.381) | 1.015 mg\cdot L (0.692) | NR | NR | H-ITZ\textsuperscript{a} | Mean (STDV) 4.429 mg\cdot h/L (1.072) | NR | NR | H-ITZ\textsuperscript{a} | Mean (STDV) 4.429 mg\cdot h/L (1.072) | NR | NR | H-ITZ\textsuperscript{a} | Mean (STDV) 4.429 mg\cdot h/L (1.072) | [40] |
| HSCT patients aged 0.9–23 years, for PK part patients aged 9.4–14.8 years | 2.5 mg/kg | PO (solution) | Mean\textsuperscript{b} 29 kg | 6 | MD (after third IV dose) | ITZ\textsuperscript{a} | Mean (STDV) 4.429 mg\cdot h/L (1.072) | NR | NR | ITZ\textsuperscript{a} | Mean (STDV) 4.429 mg\cdot h/L (1.072) | NR | NR | ITZ\textsuperscript{a} | Mean (STDV) 4.429 mg\cdot h/L (1.072) | 42.837 mg\cdot h/L (24.746) | AUC\textsubscript{0–24,SS} | 39.5 h (33.5) | CL\textsubscript{SS} | 0.1313 L/h/kg (0.05652) | CL\textsubscript{SS} | 0.07969 L/h/kg (0.02662) | CL\textsubscript{SS} | 5.659 L/kg (2.341) | [40] |
| Prophylaxis: PO (solution) Treatment: IV | 2.5 mg/kg every 12 h for 2 days Followed by treatment with 5 mg/kg every 12 h for 2 days, and a maintenance dose of 5 mg/kg daily | 6 | MD (after third IV dose) | 6 | MD (after third IV dose) | ITZ\textsuperscript{a} | Mean (STDV) 4.429 mg\cdot h/L (1.072) | NR | NR | ITZ\textsuperscript{a} | Mean (STDV) 4.429 mg\cdot h/L (1.072) | NR | NR | ITZ\textsuperscript{a} | Mean (STDV) 4.429 mg\cdot h/L (1.072) | 42.837 mg\cdot h/L (24.746) | AUC\textsubscript{0–24,SS} | 39.5 h (33.5) | CL\textsubscript{SS} | 0.1313 L/h/kg (0.05652) | CL\textsubscript{SS} | 0.07969 L/h/kg (0.02662) | CL\textsubscript{SS} | 5.659 L/kg (2.341) | [40] |

\textsuperscript{a}H-ITZ = hydriッド itraconazole

\textsuperscript{b}Mean\textsuperscript{b} = Mean (SD)
| Population                  | Dose                        | Formulation | Weight                  | N  | SD, FD, or MD | Pharmacokinetic parameters | AUC | $T_{1/2}$ | CL | $V_d$ | References |
|-----------------------------|-----------------------------|-------------|-------------------------|----|---------------|-----------------------------|-----|-----------|----|------|------------|
| CF patients aged < 16 years | 2.5 mg/kg every 12 h for 14 days | PO (solution) | Median(range) 16.6 kg/m² (15–19.7) BMI | 5  | FD Day 1      | ITZ* Mean (STDV) 0.133 mg/L (0.135) $C_{\text{max}}$ | NR | NR       | NR | NR   | [41]       |
|                             |                             |             |                         |    |               | H-ITZ* Mean (STDV) 0.230 mg/mL (0.141) $C_{\text{max}}$ | NR | NR       | NR | NR   |            |
|                             |                             |             |                         |    |               | ITZ* Mean (STDV) 0.119 mg/L (0.0834) $C_{\text{max}}$ | ITZ* Mean (STDV) 0.119 mg/L (0.0834) $C_{\text{min}}$ | NR | NR       | NR | NR   |            |
|                             |                             |             |                         |    |               | H-ITZ* Mean (STDV) 0.278 mg/mL (0.161) $C_{\text{max}}$ | H-ITZ* Mean (STDV) 0.278 mg/mL (0.161) $C_{\text{min}}$ | NR | NR       | NR | NR   |            |
Table 6 (continued)

| Population | Dose | Formulation | Weight | N  | SD, FD, or MD | Pharmacokinetic parameters | References |
|------------|------|-------------|--------|----|---------------|----------------------------|-------------|
|            |      |             |        |    |               | \( C_{\text{max}} \) | \( C \) | \( T_{\text{max}} \) | AUC | \( T_{1/2} \) | CL | \( V_d \) |       |
| Infants and children aged 0.5–12 years with hematological malignancy or liver transplantation with mucosal fungal infection or at risk for IFD | 5 mg/kg of body weight once daily for 2 weeks | PO (oral solution) | Mean (STDV) 16.9 kg (1.7) | 26 | FD | Day 1 | 0.5–2 years | 2–5 years | 5–12 years | ITZ\textsuperscript{a} | Mean (STDV) | 0.138 mg/L (0.091) | 0.314 mg/L (0.105) | 0.298 mg/L (0.292) | \( C_{\text{max}} \) | NR | NR | ITZ\textsuperscript{a} | Mean (STDV) 1.340 mg\( \text{h/L} \) (0.780) | 2.740 mg\( \text{h/L} \) (1.080) | 2.010 mg\( \text{h/L} \) (1.380) | AUC\textsubscript{0–24} | [42] |
|            |      |             |        |    | Day 14 | 0.5–2 years | 2–5 years | 5–12 years | H-ITZ\textsuperscript{a} | Mean (STDV) | 0.179 mg/L (0.101) | 0.493 mg/L (0.106) | 0.447 mg/L (0.365) | \( C_{\text{max}} \) | NR | NR | H-ITZ\textsuperscript{a} | Mean (STDV) | 2.340 mg\( \text{h/L} \) (1.490) | 6.730 mg\( \text{h/L} \) (1.950) | 4.920 mg\( \text{h/L} \) (4.390) | AUC\textsubscript{0–24} |     |
| MD         |      |             |        |    | Day 14 | 0.5–2 years | 2–5 years | 5–12 years | ITZ\textsuperscript{a} | Mean (STDV) | 0.571 mg/L (0.416) | 0.534 mg/L (0.431) | 0.631 mg/L (0.358) | \( C_{\text{max}} \) | ITZ\textsuperscript{a} | Mean (STDV) | 0.159 ng/mL (0.218) | 0.179 ng/mL (0.101) | 0.223 ng/mL (0.145) | pre-dose concentration | ITZ\textsuperscript{a} | Mean (STDV) | 6.930 mg\( \text{h/L} \) (5.830) | 7.330 mg\( \text{h/L} \) (5.420) | 8.770 mg\( \text{h/L} \) (5.050) | AUC\textsubscript{0–24} |     |
|            |      |             |        |    |       | 0.5–2 years | 2–5 years | 5–12 years | H-ITZ\textsuperscript{a} | Mean (STDV) | 0.690 mg/L (0.445) | 0.687 mg/L (0.419) | 0.699 mg/L (0.234) | \( C_{\text{max}} \) | H-ITZ\textsuperscript{a} | Mean (STDV) | 0.308 mg/L (0.436) | 0.487 mg/L (0.314) | 0.437 mg/L (0.246) | pre-dose concentration | H-ITZ\textsuperscript{a} | Mean (STDV) | 13.200 mg\( \text{h/L} \) (11.400) | 15.400 mg\( \text{h/L} \) (9.110) | 13.450 mg\( \text{h/L} \) (7.190) | AUC\textsubscript{0–24} |     |

\( \text{ITZ} \) and \( \text{H-ITZ} \) are the abbreviations used for itraconazole and hydroxyitraconazole, respectively.
Table 6 (continued)

| Population                          | Dose                      | Formulation                  | Weight | N  | SD, FD, or MD | Pharmacokinetic parameters                                                                 |
|-------------------------------------|---------------------------|------------------------------|--------|----|---------------|-------------------------------------------------------------------------------------------|
| Cancer patients at risk for IFD     | 2.5 mg/kg PO every 12 h   | PO (oral solution)           | NR     | 17 | MD            | ITZ<sup>a</sup> Mean (STDV) 0.599 mg/mL (0.231) 1.090 mg/mL (0.383)                        |
|                                     |                           |                              |        |    |               | C<sub>max</sub> day 7 ITZ<sup>a</sup> Mean (STDV) 0.678 mg/mL (0.285)                      |
|                                     |                           |                              |        |    |               | C<sub>min12h</sub> day 7 ITZ<sup>a</sup> Mean (STDV) 0.711 mg/mL (0.251)                   |
|                                     |                           |                              |        |    |               | 1.072 mg/mL (0.408)                                                                  |
|                                     |                           |                              |        |    |               | C<sub>max</sub> day 15 H-ITZ<sup>a</sup> Mean (STDV) 1.524 mg/mL (0.770)                  |
|                                     |                           |                              |        |    |               | C<sub>max</sub> day 7 H-ITZ<sup>a</sup> Mean (STDV) 1.024 mg/mL (0.351)                  |
|                                     |                           |                              |        |    |               | 1.275 mg/mL (0.449)                                                                  |
|                                     |                           |                              |        |    |               | 2.180 mg/mL (0.753)                                                                  |
|                                     |                           |                              |        |    |               | C<sub>ssmin</sub> H-ITZ<sup>a</sup> Mean (STDV) 14 days (8) 11 days (5) 13 days (4)   |
|                                     |                           |                              |        |    |               | T<sub>CSS</sub> H-ITZ<sup>a</sup> Mean (STDV) 28.488 mg*h/L (5.59) 36.840 mg*h/L (10.1) |
|                                     |                           |                              |        |    |               | AUC<sub>total</sub> H-ITZ<sup>a</sup> Mean (STDV) 28.488 mg*h/L (5.59) 36.840 mg*h/L (10.1) |

<sup>a</sup> Mean (STDV)
| Population                      | Dose                        | Formulation | Weight | N  | SD, FD, or MD | Pharmacokinetic parameters | References |
|--------------------------------|-----------------------------|-------------|--------|----|---------------|-----------------------------|------------|
| HIV-infected patients aged 5–18 years with oropharyngeal candidiasis | 2.5 mg/kg every 12 or 24 h | PO (oral solution) | NR    | 26 | FD            | ITZ<sup>a</sup> Mean (STDV) |            |
|                                |                             |             |        |    |               | 0.420 mg/L (0.06)           |            |
|                                |                             |             |        |    |               | 2.35 h (0.37)               |            |
|                                |                             |             |        |    |               | AUC<sub>0-24</sub> ITZ      |            |
|                                |                             |             |        |    |               | 3.720 mg*h/L (0.65)         | [44]       |
|                                |                             |             |        |    |               | T<sub>1/2</sub>             |            |
|                                |                             |             |        |    |               | 26.5 h (5.7)                |            |
|                                |                             |             |        |    |               | CL                          |            |
|                                |                             |             |        |    |               | 0.660 L/h/kg (0.17)         |            |
|                                |                             |             |        |    |               | V<sub>d,ss</sub>            |            |
|                                |                             |             |        |    |               | 18.90 L/kg (5.3)            |            |
|                                |                             |             |        |    |               | V<sub>d</sub>               |            |
|                                |                             |             |        |    |               | NR                          |            |

| MD                             | QD                          | BID         |        |    |               | ITZ<sup>a</sup> Mean (STDV) |            |
|                                |                             |             |        |    |               | 0.623 mg/L (0.14)           |            |
|                                |                             |             |        |    |               | 0.192 mg/L (0.06)           |            |
|                                |                             |             |        |    |               | 1.8 h (0.3)                 |            |
|                                |                             |             |        |    |               | AUC<sub>0-24</sub> ITZ      |            |
|                                |                             |             |        |    |               | 7.05 mg*h/L (2.06)          |            |
|                                |                             |             |        |    |               | T<sub>1/2</sub>             |            |
|                                |                             |             |        |    |               | 58.9 h (13.1)               |            |
|                                |                             |             |        |    |               | CL                          |            |
|                                |                             |             |        |    |               | 0.601 L/h/kg (0.26)         |            |
|                                |                             |             |        |    |               | V<sub>d,ss</sub>            |            |
|                                |                             |             |        |    |               | 5.11 L/kg (1.28)            |            |
|                                |                             |             |        |    |               | V<sub>d</sub>               |            |
|                                |                             |             |        |    |               | NR                          |            |

| MD                             | QD                          | BID         |        |    |               | H-ITZ<sup>a</sup> Mean (STDV) |            |
|                                |                             |             |        |    |               | 0.319 mg/L (0.04)           |            |
|                                |                             |             |        |    |               | 2.35 h (1.69)               |            |
|                                |                             |             |        |    |               | T<sub>max</sub>             |            |
|                                |                             |             |        |    |               | AUC<sub>0-24</sub> H-ITZ    |            |
|                                |                             |             |        |    |               | 5.240 mg*h/L (0.81)         |            |
|                                |                             |             |        |    |               | T<sub>1/2</sub>             |            |
|                                |                             |             |        |    |               | 26.8 h (4.0)                |            |
|                                |                             |             |        |    |               | CL                          |            |
|                                |                             |             |        |    |               | 0.339 L/h/kg (0.05)         |            |
|                                |                             |             |        |    |               | V<sub>d,ss</sub>            |            |
|                                |                             |             |        |    |               | NR                          |            |

| MD                             | QD                          | BID         |        |    |               | ITZ<sup>a</sup> Mean (STDV) |            |
|                                |                             |             |        |    |               | 0.623 mg/L (0.14)           |            |
|                                |                             |             |        |    |               | 1.340 mg/L (0.22)           |            |
|                                |                             |             |        |    |               | 0.192 mg/L (0.06)           |            |
|                                |                             |             |        |    |               | 1.8 h (0.3)                 |            |
|                                |                             |             |        |    |               | AUC<sub>0-24</sub> ITZ      |            |
|                                |                             |             |        |    |               | 7.05 mg*h/L (2.06)          |            |
|                                |                             |             |        |    |               | T<sub>1/2</sub>             |            |
|                                |                             |             |        |    |               | 58.9 h (13.1)               |            |
|                                |                             |             |        |    |               | CL                          |            |
|                                |                             |             |        |    |               | 0.601 L/h/kg (0.26)         |            |
|                                |                             |             |        |    |               | V<sub>d,ss</sub>            |            |
|                                |                             |             |        |    |               | 5.11 L/kg (1.28)            |            |
|                                |                             |             |        |    |               | V<sub>d</sub>               |            |
|                                |                             |             |        |    |               | NR                          |            |

| MD                             | QD                          | BID         |        |    |               | H-ITZ<sup>a</sup> Mean (STDV) |            |
|                                |                             |             |        |    |               | 0.552 mg/L (0.08)           |            |
|                                |                             |             |        |    |               | 1.170 mg/L (0.18)           |            |
|                                |                             |             |        |    |               | 0.385 mg/L (0.10)           |            |
|                                |                             |             |        |    |               | 1.8 h (0.3)                 |            |
|                                |                             |             |        |    |               | AUC<sub>0-24</sub> H-ITZ    |            |
|                                |                             |             |        |    |               | 6.05 mg*h/L (2.82)          |            |
|                                |                             |             |        |    |               | T<sub>1/2</sub>             |            |
|                                |                             |             |        |    |               | 55.6 h (21.3)               |            |
|                                |                             |             |        |    |               | CL                          |            |
|                                |                             |             |        |    |               | 0.160 L/h/kg (0.05)         |            |
|                                |                             |             |        |    |               | V<sub>d,ss</sub>            |            |
|                                |                             |             |        |    |               | NR                          |            |

| AUC area under the curve, AUC<sub>area</sub> | AUC<sub>area</sub> standardized to a day, BID twice daily, C<sub>avg</sub> average serum concentration, CL clearance, C<sub>max</sub> maximum serum concentration, C<sub>min</sub> minimal serum concentration, C<sub>HITZ</sub> average steady-state plasma concentration, F bioavailability, FD first dose, h hours, H-ITZ hydroxy-itraconazole, HIV human immunodeficiency virus, HSCT hematopoietic stem cell transplantation, IFD invasive fungal disease, IQR interquartile range, ITZ itraconazole, IV intravenous, MD multiple dose, N total patients, NR not reported, PO ‘per os’ (oral administration), PK pharmacokinetic, QD once daily, SD single dose, SS steady state, STDV standard deviation, T<sub>1/2</sub> elimination half-life, T<sub>max</sub> time to reach C<sub>max</sub>, t<sub>ma</sub> time to reach C<sub>max</sub>, V<sub>d</sub> volume of distribution |

<sup>a</sup>Values recalculated/adjusted from the original paper to create uniformity of units

<sup>b</sup>Error not mentioned
### Table 7  Population pharmacokinetic estimates of itraconazole

| Population | Dose          | Formulation | Weight (SD, FD, or MD) | N   | Pharmacokinetic parameters | References |
|------------|---------------|-------------|------------------------|-----|-----------------------------|------------|
|            |               |             |                        |     | AUC | T_{1/2} | T_{lag} | CL  | V1  | Q1  | V2  | Q2  | V3  | Ka | F            |
| Children at risk for IFD aged 6 months to 17 years | 2.5 mg/kg | IV | Mean (SDV) 31.1 kg (22.7) | 33  | ITZ\^{a,d} Estimated value 16.9 L/h | ITZ\^{a,d} Estimated value 63.8 L | ITZ\^{a,d} Estimated value 30.2 L/h | ITZ\^{a,d} Estimated value 134 L | ITZ\^{a,d} Estimated value 9.57 L/h | ITZ\^{a,d} Estimated value 88.1 L | NR | NR | [39] |
| Pediatric patients with CF and BMT patients aged 0.4–18 years (including 5 adults) | Median (range) 5.4 mg/kg (1.5–12.5) daily PO dose | Median (range) 29.3 kg (6.8–83.5) | 49 (including 5 adults) | MD | ITZ\^{b} Mean 19.1 min (3.3) | ITZ\^{b} Mean 35.5 L/h (13.8) | ITZ\^{b} Mean 627.0 L (27.3) | NR | NR | NR | NR | Mean (RSE%) 0.09 1/h (21.7) | Mean (RSE%) 0.55 1/h (12.7) | Capsule F_{relative} Mean (RSE%) 0.96 1/h (67.4) | [45] |

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AUC area under the curve, BMT bone marrow transplantation, CF cystic fibrosis, CL clearance, F bioavailability, FD first dose, H-ITZ hydroxy-itraconazole, IFD invasive fungal disease, ITZ itraconazole, K_{\text{a}} rate of oral bioavailability, MD multiple dose, N number of patients, NR not reported, Q1 intercompartmental clearance (compartments 1–2), Q2 intercompartmental clearance (compartments 1–3), RSE relative standard error, SD single dose, STDV standard deviation, T_{1/2} elimination half-life, T_{lag} lag time, V1 volume of distribution (central compartment 1), V2 volume of distribution (peripheral compartment 2), V3 volume of distribution (peripheral compartment 3)

\(^{a}\)Values scaled to a body weight of 30 kg

\(^{b}\)Values scaled to a body weight of 70 kg

\(^{c}\)Relative bioavailability of capsules compared to solution

\(^{d}\)Error was not reported
### Table 8 Pharmacokinetic models of itraconazole

| Population | Subjects | Samples | Program | Covariates tested | Compartments | PO/IV | Covariates in final model | References |
|------------|----------|---------|---------|-------------------|--------------|-------|--------------------------|------------|
| Children at risk for IFD aged 6 months to 16 years | 33 | NR | NON-MEM | WT | 3, with first-order elimination | IV | WT normalized to 30 kg | [39]* |
| Pediatric patients with CF and BMT aged 0.4–18 years (including 5 adults aged 19–30 years) | 49 (29 CF of which 5 adults and 20 BMT) | 227 | NON-MEM | Total WT, lean WT, age, disease, and effect of acidic beverage and food intake, sex, disease category | 1-compartment with first-order absorption for ITZ and first-order elimination to H-ITZ and a 1-compartment with first-order elimination pathway for H-ITZ | ITZ, ITZ, ITZ, ITZ, ITZ, ITZ, ITZ, ITZ, ITZ | ITZ, ITZ, ITZ, ITZ, ITZ, ITZ, ITZ, ITZ, ITZ | [45] |

*BMT bone marrow transplantation, CF cystic fibrosis, CL clearance, F bioavailability, H-ITZ hydroxy-itraconazole, IFD invasive fungal disease, ITZ itraconazole, K<sub>a</sub> rate of oral bioavailability, N number of patients, NR not reported, Q<sub>1</sub> intercompartmental clearance (compartments 1–2), Q<sub>2</sub> intercompartmental clearance (compartments 1–3), STDV standard deviation, V<sub>1</sub> volume of distribution (central compartment 1), V<sub>2</sub> volume of distribution (peripheral compartment 2), V<sub>3</sub> volume of distribution (peripheral compartment 3), WT bodyweight

*WT is included as covariate on itraconazole parameters, however the covariate equation was not reported

*Values of exponents used for allometric scaling are not reported
patients, a median itraconazole dose of 5.4 mg/kg was given orally as capsules or solution. The vast majority of patients received itraconazole in a once-daily regimen. A one-compartment model was used with delayed absorption and included both itraconazole and hydroxy-itraconazole. The $K_p$ for the solution and capsules was 0.96 h$^{-1}$ and 0.09 h$^{-1}$, respectively. The relative $F$ of capsules was 0.55 compared to the solution. Clearance and $V_d$ of itraconazole were allometrically scaled to a total body weight of 70 kg [45]. Values of exponents used for allometric scaling were not reported.

5.3 Summary of Findings and Recommendations

Pharmacokinetic studies of itraconazole are limited in pediatric patient populations and are lacking in neonates. Future research should focus on retrieving pharmacokinetic data in these patient populations and should address the $F$ of the different itraconazole formulations.

The itraconazole oral solution is the preferred formulation, as the relative $F$ was 45% higher compared with itraconazole capsules. Given the unknown absolute $F$ and the difference in $F$ of the oral formulations, dosing of itraconazole and switching between formulations should be accompanied by therapeutic drug monitoring. Furthermore, a twice-daily itraconazole regimen instead of a once-daily regimen is suggested to optimize itraconazole exposure.

Non-compartmental analyses suggest a great extent of variability across different age groups, attributable to both CL and $V_d$. Differences in studies preclude final conclusions and warrant further investigation. Pediatric patients with CF might need a higher itraconazole dose as a considerably lower exposure is reported compared with patients without CF.

Population pharmacokinetic studies included allometrically scaled bodyweight on itraconazole pharmacokinetic parameters. As itraconazole and hydroxy-itraconazole are highly bound to plasma protein, the unbound drug concentrations of itraconazole and hydroxy-itraconazole could be interesting variables for future research specifically in the critically ill population. Research in critically ill populations might be of interest in resource-poor countries where posaconazole and voriconazole may not be available.

Itraconazole is not approved for patients aged < 18 years in the labels, but international guidelines provide a dose recommendation for patients aged ≥ 2 years for both prophylaxis and treatment. Agreement between labels and guidelines is important for clinical practice and needs to be established.

6 Voriconazole

Voriconazole was both European Medicines Agency and FDA approved in 2002 for adult patients and has been available as oral tablets, oral suspension, and powder for concentrate for solution [5, 46]. The current approved indications for both adult and pediatric patients aged ≥ 2 years are treatment of invasive aspergillosis, candidemia in patients without neutropenia, esophageal candidiasis, infections caused by Scedosporium and Fusarium species [5, 46], fluconazole-resistant invasive Candida infections, and prophylaxis of IFD in high-risk allogenic HSCT [46]. The labels, the pediatric ESCMID-ECMM guideline for invasive aspergillosis, and the pediatric ESCMID invasive candidiasis guideline provide dose recommendations for pediatric patients aged ≥ 2 years. For prophylaxis and treatment of both invasive aspergillosis and candidiasis, a loading dose of 9 mg/kg twice daily on day 1, followed by 8 mg/kg twice daily intravenously or 9 mg/kg (maximum 350 mg) twice daily for the oral formulations in pediatric patients aged 2–11 years or aged 12–14 years (<50 kg) is recommended. A loading dose of 6 mg/kg twice daily on day 1, followed by 4 mg/kg twice daily intravenously or 200 mg twice daily for the oral formulations is recommended in pediatric patients aged 12–14 years (≥50 kg) or aged ≥ 14–15 years [1, 2, 5, 46].

In adults, voriconazole is characterized by a $F$ of 96% for both tablets and suspension [5], which makes it possible to switch between the two available formulations. As food intake can reduce voriconazole absorption, both oral formulations are advised to be administered in a fasted state [5, 47]. The $V_d$ of voriconazole is around 4.6 L/kg. [5] The distribution of voriconazole is suggested to be extensive into different body tissues, including the cerebrospinal fluid [48] and aqueous and vitreous parts of the eye [49]. Voriconazole is bound to plasma proteins for around 58% [5]. Voriconazole is characterized by nonlinear pharmacokinetics in adult patients. The main CYP450 enzyme involved in the metabolism of voriconazole is CYP2C19 with also CYP2C9 and CYP3A4 playing a less prominent role (Table 1). Elimination via renal excretion accounts for only 2% in its unchanged form [5, 46].

6.1 Non-Compartmental Analysis of Voriconazole PK in Pediatric Patients

There are no NCA of voriconazole PK available in neonates and infants. Five NCA are available in pediatric patients aged 2–17 years. A detailed overview of the dosing regimens and voriconazole pharmacokinetic results is given in Table 9. Patients with hematological and non-hematological malignancies and patients undergoing BMT or HSCT were included in these studies. Voriconazole was administered either orally or in a combined intravenous to oral regimen. The oral voriconazole dose was from 4 to 9 mg/kg (maximum 350 mg) twice daily or was fixed at 200 or 300 mg twice daily. The intravenous voriconazole dose was from 4 to 8 mg/kg twice daily, either with or without a loading dose of 6 to 9 mg/kg twice daily [50–54].
Overall, only one study reported the F of voriconazole from 43.6 to 90.0% [52]. This F in pediatric patients was lower compared with the F of 96% seen in adults [5]. In the other studies, a lower F was hypothesized, as lower exposures were reported after oral administration compared with exposures after intravenous administration [50, 51, 54]. Unlike observations in adults where food intake reduces voriconazole absorption [5, 46], it remains unclear if the influence of food intake attributes to the variable F of voriconazole in pediatric patients. The reported lower F and subsequent lower exposure after oral administration imply that there is no bioequivalence between intravenous and oral formulations of voriconazole in pediatric patients. Two studies stratified pharmacokinetic results of voriconazole by age [52, 54]. One of these studies reported an overall comparable exposure of voriconazole in the group aged 2–5 years and aged 6–11 years after administration of 4, 6, or 8 mg/kg of voriconazole in a twice-daily intravenous to oral regimen. This study also reported a ~2.5 times increased exposure after increasing voriconazole from 4 to 8 mg/kg, suggesting non-linear PK in these pediatric patients over a dose range of 4–8 mg/kg [52]. The other study administered voriconazole according to the current labels and guidelines. For a detailed description of the dosing strategies, see Table 9. This study also reported a ~2.5 times increased exposure after increasing voriconazole from 4 to 8 mg/kg, suggesting non-linear PK in these pediatric patients over a dose range of 4–8 mg/kg [52]. The other study administered voriconazole according to the current labels and guidelines. For a detailed description of the dosing strategies, see Table 9. This study also reported a ~2.5 times increased exposure after increasing voriconazole from 4 to 8 mg/kg, suggesting non-linear PK in these pediatric patients over a dose range of 4–8 mg/kg [52].

6.2 Population Pharmacokinetic Analysis of Voriconazole in Pediatric Patients

There are no population pharmacokinetic analyses of voriconazole available in neonates. One study included infants, but did not describe the pharmacokinetic results for this population separately [55]. In total, nine studies were performed in pediatric patients aged 0.8–21 years [55–63], of which two studies pooled data of three earlier published studies [57, 62] and included data of healthy adult patients [57]. A detailed overview of the dosing regimens and voriconazole pharmacokinetic results is given in Table 10. These studies included immunocompromised patients with hematological or non-hematological diseases, immunodeficiency or autoimmune diseases, liver transplantation, CF, other infections/diseases or undergoing HSCT or BMT [55–63]. Voriconazole was administered either intravenously [55, 61, 63], orally [55], or in a combined intravenous to oral regimen [56–60, 62]. All studies reported PK of voriconazole in a two-compartment model [55–62] and one study included also one compartment for the metabolite of voriconazole [63]. The models included delayed absorption [55, 57, 59] and first-order absorption [55–60, 62] and either linear [61], nonlinear [55, 56, 58, 60, 62], or mixed linear and nonlinear elimination [57, 59]. In one study, voriconazole elimination was included as linear CL but in addition also as non-linear CL to its metabolite [63]. Two other studies included both concentration- and time-dependent voriconazole elimination [57, 59]. The PK models and covariates tested are summarized in Table 11.

Seven studies in pediatric patients administered either an oral solution or tablets of voriconazole in which the F was from 44.6 to 85% [55–60, 62]. The F found in these studies was also lower compared with the F of 96% reported in adults [5]. Similar to findings in the NCA, it remains unclear if the influence of food was attributed to this difference. The $K_{a}$ had a range of 0.43–1.53 h⁻¹ [55–60, 62]. Allometrically scaled bodyweight with fixed exponents [56–60, 63] was added on either CL [57, 59, 63], $V_d$ [57–60, 63], and/or maximum rate of enzyme activity [56–60, 63]. Two studies included patients aged <2 years [55, 63], of which one study had sufficient information to include a maturation factor to the pharmacokinetic model [63]. Two other studies incorporated the CYP2C19 genotype [61, 62], alanine aminotransferase (ALT) [61, 62], and alkaline phosphatase on CL. In these studies, the CYP2C19 genotype in the combined group of heterozygous extensive/poor CYP2C19 metabolizers [61, 62], ALT [61, 62], and alkaline phosphatase [61] significantly decreased CL, but according to the authors these variables were not predictive for voriconazole CL [61, 62]. Other covariates included linearly scaled weight and age on CL and $V_d$ [55].

6.3 Physiologically Based PK of Voriconazole

One physiologically based pharmacokinetic model was developed for voriconazole in children. The physiologically based pharmacokinetic-derived values from the initial oral model showed an overprediction for $F$, area under the curve (AUC), and maximum serum concentration in children, which decreased substantially after adding intestinal CL to the model. Intestinal first-pass metabolism might explain the lower bioavailability of voriconazole in children compared with adults [64].

6.4 Summary of Findings and Recommendations

The PK of voriconazole in neonates and infants and children aged <2 years is lacking, and future studies should take these patient populations into account. Future research
| Population                                      | Dose                                                                 | Formulation | Weight | N     | SD, FD, or MD | Pharmacokinetic parameters | References |
|------------------------------------------------|-----------------------------------------------------------------------|-------------|--------|-------|---------------|----------------------------|------------|
| Hematology or HSCT pediatric patients aged 2 to <12 years | 7 mg/kg IV every 12 h for 7 days followed by 200 mg PO every 12 h for 6.5 days |              | 18.9 kg (10.8–54.5) | 40    | IV and PO     | Median (range) |                          |
| Group A: 7 mg/kg IV every 12 h                      | 24.2 kg (13–41)                                                      |             | 12 (9 in group A and 3 in group B) |       |               | 11.4 µg/mL (2.9–19.2) | [51]        |
| Group B: 6 mg/kg IV every 12 h                      | 5.8 µg/mL (2.4–17.2)                                                 | Group A     | 1.1 h (1.0–1.1) |       |               | 2.2 µg/mL (1.1–3.5) |            |
| MD                                              | Group B 3 Group A Group B                                             |             | 10.9 h (3.1–29.2) |       |               | 49.3 µg*h/mL (4.7–106.6) |            |
| Group B: 192.1 mL/h/kg                             | 192.1 mL/h/kg (12.6–41.5)                                            |             | 7.7 h (4.2–14.6) |       |               | 141.9 mL/h/kg (65.7–1483.1) |            |
| Group B: 192.1 mL/h/kg                             | 192.1 mL/h/kg (12.6–41.5)                                            |             | 7.7 h (4.2–14.6) |       |               | 141.9 mL/h/kg (65.7–1483.1) |            |
| Group B: 1.07 h (0.73–8.03)                        | 0.49 µg/mL (0.04–128)                                                |             | 7.00 µg*h/mL (2.43–36.6) |       |               | 21.8 µg*h/mL (5.02–162) | [51]        |
| Group B: 192.1 mL/h/kg                             | 192.1 mL/h/kg (12.6–41.5)                                            |             | 7.7 h (4.2–14.6) |       |               | 141.9 mL/h/kg (65.7–1483.1) |            |
| Group B: 192.1 mL/h/kg                             | 192.1 mL/h/kg (12.6–41.5)                                            |             | 7.7 h (4.2–14.6) |       |               | 141.9 mL/h/kg (65.7–1483.1) |            |
| Population                        | Dose                       | Formulation | Weight | N  | SD, FD, or MD | Pharmacokinetic parameters | Cmax | Cmin | Tmax | AUC | T1/2 | CL | Vd | F   | References |
|----------------------------------|----------------------------|-------------|--------|----|---------------|-----------------------------|------|------|------|-----|------|----|----|-----|------------|
| Hematopoietology, BMT and HSCT   | 2–5 years; every 12 h;     | IV and PO   | Mean (range) | 48 | 24.3 kg       |                              | 3.352 µg/mL | 1.97 h (0) | 1.36 h (15) | 11.722 µg*h/mL | 1.97 h (0) | 1.36 h (16) | 21.931 µg*h/mL | 24.047 µg*h/mL | (13.0–54.9) |
| pediatric patients aged 2 to < 12 years | days 2–4; 4 mg/kg IV every 12 h; days 5–8; 6 mg/kg IV every 12 h; days 9–11; 4 mg/kg PO every 12 h | Cohort 1 MD | 20.8 kg | 4 mg/kg PO every 12 h; from day 12: 4 mg/kg PO every 12 h | 4.690 µg/mL | (111) | 1.97 h (0) | 1.36 h (15) | 21.931 µg*h/mL | 24.047 µg*h/mL | (10.8–37.6) |
| Hematopoietology, BMT and HSCT   | 2–5 years; every 12 h;     | IV and PO   | Mean (range) | 48 | 24.3 kg       |                              | 3.352 µg/mL | 1.97 h (0) | 1.36 h (15) | 11.722 µg*h/mL | 1.97 h (0) | 1.36 h (16) | 21.931 µg*h/mL | 24.047 µg*h/mL | (13.0–54.9) |
| pediatric patients aged 2 to < 12 years | days 2–4; 4 mg/kg IV every 12 h; days 5–8; 6 mg/kg IV every 12 h; days 9–11; 4 mg/kg PO every 12 h | Cohort 1 MD | 20.8 kg | 4 mg/kg PO every 12 h; from day 12: 4 mg/kg PO every 12 h | 4.690 µg/mL | (111) | 1.97 h (0) | 1.36 h (15) | 21.931 µg*h/mL | 24.047 µg*h/mL | (10.8–37.6) |
| Cohort 2 MD                      | 2–5 years; every 12 h;     | IV and PO   | Mean (range) | 48 | 24.3 kg       |                              | 3.352 µg/mL | 1.97 h (0) | 1.36 h (15) | 11.722 µg*h/mL | 1.97 h (0) | 1.36 h (16) | 21.931 µg*h/mL | 24.047 µg*h/mL | (13.0–54.9) |
|                                    | days 2–4; 4 mg/kg IV       |            |         |     |               |                              | 4.690 µg/mL | (111) | 1.97 h (0) | 1.36 h (15) | 21.931 µg*h/mL | 24.047 µg*h/mL | (13.0–54.9) |
|                                    | every 12 h; days 5–8; 6 mg/kg IV every 12 h; days 9–11; 4 mg/kg PO every 12 h | Cohort 2 MD | 20.8 kg | 4 mg/kg PO every 12 h; from day 12: 4 mg/kg PO every 12 h | 4.690 µg/mL | (111) | 1.97 h (0) | 1.36 h (15) | 21.931 µg*h/mL | 24.047 µg*h/mL | (10.8–37.6) |
| Population                              | Dose                        | Formulation | Weight       | N  | Pharmacokinetic parameters | SD, FD, or MD | References |
|-----------------------------------------|-----------------------------|-------------|--------------|----|-----------------------------|---------------|------------|
| Immunocompromised                       | 2–12 years or 12–15 years   | IV and PO   | Mean (range) | 21 | Median (range)              | MD IV         | [54]       |
| hematologic oncology                    | (< 50 kg); day 1: 9 mg/kg IV| every 12 h  | 30.4 kg      |    | Median (range)              | 2.89 µg/mL    |            |
| and non-hematologic oncology            | days 2–7: 8 mg/kg IV        | every 12 h  | (11.5–55.2)  |    | (0.596–9.36)               |               |            |
| Japanese pediatric patients aged 2 to   | 12 h; days 8–14: 9 mg/kg PO| every 12 h  | 7.72 µg/mL   |    | 2.96 h (0.950–4.00)        |               |            |
| < 15 years                              | (maximum 350 mg)            | every 12 h  | (4.62–12.6)  |    | 4.00 h (2.92–4.20)         |               |            |
| MD PO                                   | 2 to < 12 years             |             | Median (range) |    | 1.34 h (1.00–1.67)         |               |            |
| (≥ 50 kg); day 1: 6 mg/kg every 12 h    | 12–14 years (< 50 kg)      |             | Median (range) |    | 2.96 h (0.950–4.20)        |               |            |
| days 2–7: 4 mg/kg IV every 12 h         | 12–14 years (≥ 50 kg)      |             | Median (range) |    | 1.34 h (1.00–1.67)         |               |            |
| All                                     | days 8–14: 200 mg PO every  |             | Median (range) |    | 2.96 h (0.950–4.20)        |               |            |
| 12 h                                    | 12 h for the next 6 days    |             | Median (range) |    | 1.34 h (1.00–1.67)         |               |            |
| and were switched to 300 mg PO every    | and were switched to 300 mg |             | Median (range) |    | 2.96 h (0.950–4.20)        |               |            |
| 12 h                                    | PO every 12 h               |             | Median (range) |    | 1.34 h (1.00–1.67)         |               |            |
| Hematopoietic and HSCT adolescents      | 6 mg/kg IV every 12 h on day | IV and PO   | Median       | 26 | Median (range)              | FD/MD         | [50]       |
| aged 12 to 17 years                     | 1 followed by 4 mg/kg IV    |             | 57.1 kg      |    | 1.09 h (0.917–3.78)        |               |            |
|                                         | every 12 h for the next 6   |             | (30.4–922)   |    | 1.00 h (0.950–2.03)        |               |            |
|                                         | days and were switched to    |             | Median (range) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         | 300 mg PO every 12 h         |             | Median (range) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |
|                                         |                             |             | 1.97 h (1.90–2.08) |    | 1.00 h (0.950–2.03)        |               |            |

AUC area under the curve, BMAT bone marrow transplantation, C<sub>max</sub> average plasma concentration, CL clearance, C<sub>min</sub> maximum concentration in blood/plasma, C<sub>min</sub> minimal concentration in blood/plasma, F bioavailability, FD first dose, h hours, HSCT hematopoietic stem cell transplantation, IQR interquartile range, IV intravenous, MD multiple dose, N total patients, NR not reported, PO 'per os' (oral administration), SD single dose, SS steady state, T<sub>1/2</sub> elimination half-life, T<sub>max</sub> time to reach C<sub>max</sub>, V<sub>d</sub> volume of distribution

<sup>a</sup>Values recalculated/adjusted from the original paper to create uniformity of units

<sup>b</sup>Values from 1 patient
### Table 10 Population pharmacokinetic estimates of voriconazole

| Population                                                                 | Dose                                                                 | Formulation            | Weight                  | N  | SD, FD, or MD | Pharmacokinetic parameters |
|----------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------|-------------------------|----|---------------|-----------------------------|
|                                                                            |                                                                      |                        |                         |    |               | AUC, T, Tlag, CL, V1        |
| Hemato-oncology patients and patients with other diseases aged 8–15 years  | NR                                                                  | IV and PO              | NR                      | 55 | MD            | NR, NR, NR, NR              |
| Immuno compromised children and adolescents aged 2–17 years (also adult data included) | 2 to < 12 years IV: day 1: 6 mg/kg every 12 h; days 2–4: 3 mg/kg every 12 h; days 5–8: 4 mg/kg every 12 h | IV and PO (tablet and suspension) | Median (range)           | 112 children | 26 adolescents | 35 adults                   |
|                                                                            |                                                                      |                        | 20.1 kg (10.8–54.9)    |    |               | Value (RSE%)                |
|                                                                            |                                                                      |                        | 57.1 kg (30.4–92.2)    |    |               | T50 = 2.41 h (6.6)          |
|                                                                            |                                                                      |                        | 76.0 kg (49.0–97.0)    |    |               | 0.949 \cdot (1 + (–0.874 \cdot (1 – STDY5,adult)))^c |
|                                                                            |                                                                      |                        |                         |    |               | 6.16 \times \frac{WT}{70}^{0.75} |
|                                                                            |                                                                      |                        |                         |    |               | 79.0 \times \frac{WT}{70}    |
| Immuno compromised children and adolescents aged 2 to 12 years IV and PO:  | 2 to 12 years IV and PO: day 1: 6 mg/kg IV every 12 h; days 2–4: 4 mg/kg IV every 12 h; days 5–8: 6 mg/kg IV every 12 h; days 9–12: 4 mg/kg PO every 12 h |                       |                         |    |               |                             |
| Or days 1–4: 6 mg/kg IV every 12 h; days 5–8: 8 mg/kg IV every 12 h; days 9–12: 6 mg/kg PO every 12 h | Or days 1–7: 7 mg/kg IV every 12 h; days 8–14: 200 mg PO every 12 h |                       |                         |    |               |                             |
| 12 to < 17 years IV and PO: day 1: 6 mg/kg IV every 12 h; days 2–7: 4 mg/kg IV every 12 h; days 8–14: 300 mg PO every 12 h | Adults: day 1: 6 mg/kg IV every 12 h; days 2–7: 4 mg/kg IV every 12 h; days 8–14: 200 mg PO every 12 h |                       |                         |    |               |                             |
Table 10 (continued)

| Population | Dose | Formulation | Weight | N  | SD, FD, or MD | Pharmacokinetic parameters |
|------------|------|-------------|--------|----|---------------|-----------------------------|
|            |      |             |        |    |               | AUC | T  | Tlag | CL  | V1 |
| HSCT patients aged ≤ 12 years: 7 mg/kg every 12h IV > 12 years: 6 mg/kg every 12h for the first 24 h, followed by 4 mg/kg every 12 h thereafter If possible switched to PO with a fixed dose of 200 mg every 12 h for all age groups | IV and PO | Value (range) | 23 | MD | NR | NR | NR | NR | Value (RSE%) |
| ≤ 12 years: 7 mg/kg every 12h IV | | ≤12 years: 27 kg (7-44) | | | | | | | 228 L/(70kg (13.5) |
| > 12 years: 6 mg/kg every 12h | | > 12 years: 56 kg (39-85) | | | | | | | |
| Patients with hematological malignancies or other diseases aged 2 to <12 years | IV and PO (suspension) | Median (range) | 82 | MD | NR | NR | NR | NR | Value (RSE%) |
| Study A | 22.8 kg (10.8-54.9) | | | | | | | | 0.582 L/h/kg (19) |
| Study B/C | 228 L/70kg (13.5) | | | | | | | | CL in EMs Decreased in CL for HEMs/PMs (35.5) |
| Immunocompromised Japanese children aged 2 to <15 years | IV and PO (suspension) | Median (range) | 21 | MD | NR | Estimate (RSE%) | Estimate (RSE%) | CL = 0.02 × (WT/70)0.75 | 75.0 × (WT/70) |
| 2–12 and 12–15 years (<50 kg): day 1: 9 mg/kg IV every 12h; day 2-7: 8 mg/kg IV every 12h; days 8-14: 9 mg/kg PO every 12 h (maximum 350 mg) | | 31.5 kg (11.5-55.2) | | | | 2.45 h (6.3) | 0.121 h (2.8) | | |
| 12–5 years (≥50 kg): day 1: 6 mg/kg every 12h IV; days 2–14: 9 mg/kg IV every 12 h; days 8-14: 200 mg PO every 12 h | | | | | | | | | |
| Patients with hematological malignancies or other diseases aged 2 to <12 years (and healthy adults) | IV and PO | Mean (range) | 141 | MD | NR | NR | NR | NR | WtMedian (95% CI) |
| Children: mean dose (range) of 5.6 mg/kg (3.0-8.4) | Children | 22.7 kg (10.8-54) | | | | | | | 1.20 L/kg (1.09–1.31) |
| Adults: mean dose (range) of 2.8 mg/kg (1.8-4.4) | Adults | 75.8 kg (49-97) | | | | | | | Vcentral |
### Table 10 (continued)

| Population                                                                 | Dose                                                                 | Formulation | Weight   | N       | SD, F.D. or MD | Pharmacokinetic parameters |
|---------------------------------------------------------------------------|----------------------------------------------------------------------|-------------|----------|---------|----------------|----------------------------|
|                                                                           |                                                                     |             |          |         |                | AUC | T | Tlag | CL | Geometric mean (GRSE%) | Geometric mean (GRSE%) | Geometric mean (GRSE%) |
| Immuno-compromised with hematological and non-hematological malignancies, liver transplantation, CF, immunodeficiency or autoimmune disease and oncology patients aged 0.8–20.5 years | IV: 150 mg (55–180), 6.0 mg/kg (3.4–10.5) PO or nasogastrically: 200 mg (30–600), 5.3 mg/kg (2.0–129) | IV and PO   | Median (range) | 40      | MD < 12 years | 4.17 h (13) | 4.14 h (11) | 0.32 L/kg/h (125) | 0.27 L/kg (188) | 0.17 L/kg (188) |
| Immuno-compromised children aged 2–11 years                                | SD: 3 or 4 mg/kg                                                   | IV          | Mean (range) | 11 (SD) | MD            | NR | NR | Value (RSE%)f | Value (RSE%)f | Decreased CL in HEMs/PMs of 46% |
|                                                                            | MD: day 1: loading dose of 6 mg/kg every 12 h; days 2–4: 3 mg/kg every 12 h; days 4–8: 4 mg/kg every 12 h |
| Patients undergoing HSCT aged < 2 to 21 years                              | IV                                                                 | NR          | 59        | MD      | NR            | NR | NR | NR | 4.60 × (WT/70)0.75 × [(AgeHill coef)/ (AgeHill coef + TMHill coef)] |
|                                                                            |                                                                 |             |           |         |               |    |    |    | 52.4 × (WT/70)1 |

Pharmacokinetic parameters

| Q1 | V2 | Q2 | V3 | K | F | Vmax | Vmax,inf | K\textsubscript{m} |
|----|----|----|----|---|---|------|----------|---------------|
| NR | NR | NR | NR | WtMedian (95% CI) 0.79 1/h (0.58–0.86) | WtMedian (95% CI) 0.48 (0.40–0.56) | WtMedian (95% CI) 1.24 mg/h/kg0.75 (0.79–180) | NR | WtMedian (95% CI) 5.3 mg/L (2.94–5.98) |

\[V_{max} = 1.50 + (−0.390 \times \text{AGE < 12}) \times \log(\text{Y}) \times \text{K}\textsubscript{m}\text{, inf}\]
| Pharmacokinetic parameters | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | References |
|----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Q1                         | 21.9 L/h/70kg (19.7) | 1130 L/70 kg (22.6) | 1.19 L/h (-) | 59.4 % (17.8) | 51.5 mg/h/70kg (15) | 1.15 mg/L (-) | 1.5 mg/L (-) Fixed |
| Q2                         | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | [58] |
| V2                         | 24.6 × (WT/70)0.75 | 101 × (WT/70) | NR NR | Estimate (RSE%) | 1.38 L/h (14) | 118 × (WT/70)0.75 | Estimate (RSE%) | 2.61 (19) | 118 × (WT/70)0.75 | [59] |
| V3                         | NR NR | NR NR | WtMedian (95% CI) | 1.35 L/h (1.14-1.78) | 1.82 mg/h/kg0.75 (0.52-3.09) | WtMedian (95% CI) | 1.54 mg/L (1.06-1.72) |
| K                          | 0.40 L/h (0.37-0.43) | 0.15 L/h (0.12-0.17) | 0.85 (0.77-0.89) | 1.82 mg/h/kg0.75 (0.52-3.09) | WtMedian (95% CI) | 1.54 mg/L (1.06-1.72) |
| K                             | Geometric mean (GRSE%) | Geometric mean (GRSE%) | Geometric mean (GRSE%) | Geometric mean (GRSE%) | Geometric mean (GRSE%) | Geometric mean (GRSE%) | Geometric mean (GRSE%) | Geometric mean (GRSE%) | Geometric mean (GRSE%) | [55] |
| Kc                          | 0.51 L/h (164) | 75% (35) | 81% (37) | 75% (35) | 81% (37) | 75% (35) | 81% (37) | 75% (35) | 81% (37) | [55] |
| KP                          | 0.43 L/h (212) | 0.43 L/h (212) | 0.43 L/h (212) | 0.43 L/h (212) | 0.43 L/h (212) | 0.43 L/h (212) | 0.43 L/h (212) | 0.43 L/h (212) | 0.43 L/h (212) | [55] |
| Vmax, inh                   | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | Value (RSE%) | [59] |
| Value (RSE%)                | 0.64 L/h/kg (15) | 1.7 L/kg (7.5%) | 36.2 × (WT/70)0.75 | NR | Estimate (RSE%) | 1.57 mg/L (34.8) |
| Value (RSE%)                | 133 × (WT/70)0.75 | 86.7 × (WT/70) | NR NR | NR NR | NR NR | NR NR | NR NR | NR NR | [63] |

A lag, absorption lag time; AUC area under the curve; CF cystic fibrosis; CI confidence interval; CL clearance; CYP cytochrome P450; EMs homozygous extensive CYP2C19 metabolizers; F bioavailability; FD first dose; GRSE geometric relative standard error; h hours; HEMs heterozygous extensive CYP2C19 metabolizers; Hill coef Hill coefficient fixed to 1; HSCT hematopoietic stem cell transplantation; IV intravenous; K rate of oral bioavailability; Kc rate constant from central to peripheral compartment; Km Michaelis–Menten constant; Kp rate constant from peripheral to central compartment; MD multiple dose; N total patients; NR not reported; PM poor CYP2C19 metabolizers; PO ‘per os’; Q1 interscompartmental clearance; Q2 interscompartmental clearance; RSE relative standard error; SD single dose; T50 time at half of the maximum inhibition of Vmax; T1/2 elimination half-life; Tlag lag time; V1 volume of distribution of the central compartment; V2 volume of distribution of the peripheral compartment; V3 volume of distribution of the peripheral compartment; Vmax, inh maximum rate of enzyme activity; Vmax, inh maximum fraction of the Vmax inhibition; WtMedian weighted median

aValues recalculated/adjusted from the original paper to create uniformity of units
bBased on priors
cValues for STDY1,ped; STDY4,adol and STDY5,adult indicate variables of 0 or 1, dependent on the study group
dVmax, inh =100% if CYP2C19 is equal to HEM or PM
eEstimates for a typical model patient, but the typical model patient is not defined
should further focus on the highly variable $F$, differences in $F$ between the oral formulations, the linear or non-linear relationship of voriconazole elimination, and PK in critically ill pediatric patients.

None of the reports highlight the difference in $F$ of the oral solution and tablets. In contrast to adults, it seems that there is no bioequivalence between oral and intravenous formulations in pediatric patients. It is unclear if the intake of food or gastric-emptying time is (partly) responsible for this variability and/or if the influence of intestinal first-pass metabolism might play a role. These questions need to be further explored. Switching from intravenous voriconazole to oral formulations cannot be done as straightforwardly as in adults but should be accompanied by therapeutic drug monitoring.

Noncompartmental analyses report that patients aged < 12 years seem to have a higher CL and $V_c$ compared with patients aged ≥ 12 years and therefore the recommended loading dose and maintenance doses of voriconazole is higher in patients aged 2–11 years compared with those above 12 years. Some population pharmacokinetic studies reported that the CYP2C19 genotype and ALT values were significant covariates on voriconazole CL, but were not predictive for voriconazole CL. Although CYP3A19 might be correlated with voriconazole CL, upfront dose adjustments in clinical practice are not yet advised in populations with a low prevalence of homozygous allele variations. Further research is needed to explain the differences of voriconazole PK in pediatric patients, to explore the influence of CYP2C19, and to reflect on the role of ALT as a surrogate marker for liver function. Additionally, other possible elimination routes (i.e., flavin-containing monoxygenase 3 [65]) might be interesting topics to explore.

### 7 Posaconazole

In 2005, posaconazole received European Medicines Agency marketing authorization and in 2006 FDA approval for adult patients [8, 66]. The currently available formulations include a concentrate for solution for infusion, an oral suspension, and gastro-resistant tablets [66]. The FDA approved posaconazole in pediatric patients aged > 13 years for prophylaxis and treatment of invasive aspergillosis and invasive candidiasis [8], but in Europe posaconazole is not approved in pediatric patients aged < 18 years [66]. Both the new solid oral tablet and the intravenous solution of posaconazole require a loading dose of double the maintenance dose, whereas this loading dose is not of value for the marketed oral suspension. In the pediatric ESCMID-ECMM guideline for invasive aspergillosis, the recommended dose for posaconazole prophylaxis for patients aged ≥ 13 years is 300 mg once daily of the gastro-resistant tablet or a dose of 200 mg three times daily of the marketed oral suspension. For salvage therapy of a proven/probable invasive aspergillosis for patients aged ≥ 13 years, 300 mg once daily of the gastro-resistant tablet or intravenous formulation or a dose of either 400 mg twice daily or 200 mg four times daily of the marketed oral suspension is recommended [1]. The posaconazole dosing in the setting of prophylaxis for invasive aspergillosis is identical to the dosing regimen of the marketed oral suspension for prophylaxis of invasive aspergillosis [2]. All the above-mentioned guidelines recommend using the gastro-resistant tablet over the marketed oral solution because of the anticipated more favorable oral bioavailability of the gastro-resistant tablet.

The $F$ of posaconazole is only reported for adult patients receiving the gastro-resistant tablets and is around 54% [8]. As the $F$ of the marketed oral suspension is not available in the public domain, bioequivalence between the formulations cannot be assured. Both the marketed oral suspension and gastro-resistant tablets show saturable absorption, but for the gastro-resistant tablets this was only seen for daily doses above 800 mg of posaconazole [67, 68]. Absorption of the marketed posaconazole suspension is significantly influenced by food intake and administration in a fed state is advised [69]. The gastro-resistant tablets are less prone to food effects [66], but a fed state can still increase the absorption by ∼ 1.5 times [70]. The tablet cannot be broken because of the gastro-resistant coating, which makes it difficult to administer these tablets to patients who are unable to swallow. The mean apparent $V_d (V_d/F)$ of posaconazole is 287 L for the gastro-resistant tablet and the $V_d/F$ is around 1774 L for the marketed oral suspension [8]. Posaconazole penetrates into a variety of tissues, including the lung, heart, kidney, and liver, but penetrates poorly into brain tissue [71] and cerebrospinal fluid [72]. Posaconazole is bound to plasma proteins for > 98% [8]. In contrast to the other azoles, posaconazole is metabolized via uridine diphosphate glucuronosyltransferase enzymes, and particularly uridine diphosphate glucuronosyltransferase 1A4 (Table 1) [73]. About 77% of radioactive-labeled posaconazole was retrieved in the feces of which 66% was the parent compound. The formed metabolites that were excreted in the urine and feces accounted for about 17% of the radioactive-labeled posaconazole [8, 66]. Mean CL is 7.3 L/h [8].

#### 7.1 Non‑Compartmental Analysis of Posaconazole PK in Pediatric Patients

Currently, there are no NCA studies of posaconazole PK performed in neonates. A detailed overview of the dosing regimens and posaconazole PK results is given in Table 12. Three NCA were performed in immunocompromised patients aged 3 months to < 18 years. [74–76] Patients with hematological and non-hematological malignancies or
| Population               | Subjects, N | Samples, N | Program          | Covariates tested                                                        | Compartments                      | PO/IV | Compartment | Covariates in final model                                                                 | References |
|--------------------------|-------------|------------|------------------|-------------------------------------------------------------------------|-----------------------------------|--------|-------------|-------------------------------------------------------------------------------------------|------------|
| Children and adolescent cancer patients aged 8–15 years | 55          | 158        | Pmetrics         | Ethnic group, age, sex, WT, hepatic dysfunction                          | 2, with first-order absorption and nonlinear elimination | PO and IV | CL           | V1                                                                                         | NR         |
|                          |             |            |                  |                                                                         |                                    |        | V2           | Q1                                                                                         | NR         |
|                          |             |            |                  |                                                                         |                                    |        | V3           | Q2                                                                                         | NR         |
|                          |             |            |                  |                                                                         |                                    |        | K            |                                                                                             | NR         |
|                          |             |            |                  |                                                                         |                                    |        | Vmax         |                                                                                             | NR         |
|                          |             |            |                  |                                                                         |                                    |        | Vmin         |                                                                                             | Allometrically scaled bodyweight with a fixed exponent of 0.75 | [56]       |
|                          |             |            |                  |                                                                         |                                    |        | F            |                                                                                             |            |
| Immunocompromised children aged 2–17 years                                          | 2022 | 554 | NON-MEM           | Age, WT, CYP2C19 genotyping status, formulation type (POS/tablet)        | 2, with first-order absorption and mixed linear and nonlinear elimination | PO and IV | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | V2           | Q2                                                                                         | NR         |
|                          |             |            |                  |                                                                         |                                    |        | K            | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          | 35 adults   | 760        |                  |                                                                         |                                    |        | Vmax         | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | Vmin         | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | F            | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
| Immunocompromised children aged 2 to ≤ 12 years and > 12 years                          | 23           | 187        | NON-MEM           | Age, sex, WT, CRP, bilirubin, AST, ALT, GGT, AP, creatinine.              | 2, with first-order absorption and nonlinear elimination | PO and IV | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | V2           | Q2                                                                                         | NR         |
|                          |             |            |                  |                                                                         |                                    |        | K            | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | Vmax         | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | Vmin         | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | F            | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
| Immunocompromised children aged 2 to <12 years                                          | 82           | 1274       | NON-MEM           | Age, sex, WT, HT, ethnic origin, serum creatinine, AST, ALT, AP, GGT, ALB, total bilirubin, total protein levels, CYP2C19, CYP2C9 and CYP3A4 inhibitors, CYP450 inducers, leukemia, BMT, aplastic anemia, lymphoma, or other, CYP2C19 genotype status, presence of mucositis| 2, with first-order absorption and nonlinear elimination | PO and IV | WT, CYP2C19 genotype, ALT(loglinear) | WT                                                                                         | WT         |
|                          |             |            |                  |                                                                         |                                    |        | V2           | Q2                                                                                         | NR         |
|                          |             |            |                  |                                                                         |                                    |        | K            | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | Vmax         | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | Vmin         | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | F            | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
| Immunocompromised Japanese children aged 2 to <15 years                                   | 21           | 276        | NON-MEM           | WT, age, sex, CYP2C19 genotyping status, liver function parameters       | 2, with first-order absorption and nonlinear elimination | PO and IV | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | V2           | Q2                                                                                         | NR         |
|                          |             |            |                  |                                                                         |                                    |        | K            | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | Vmax         | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | Vmin         | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
|                          |             |            |                  |                                                                         |                                    |        | F            | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR         |
| Population | Subjects, N | Samples, N | Program | Covariates tested | Compartments | PO/IV | Covariates in final model | References |
|------------|-------------|------------|---------|-------------------|---------------|-------|-------------------------|------------|
| Patients with hematologic malignancies or other diseases aged 2 to <12 years (and healthy adults) | 141 | Mean (STDEV) | WT, age, allometric scaling | 2, with first-order absorption and nonlinear elimination | PO and IV | NR | Allometrically scaled WT with a fixed exponent of 1 | [60] |
| Immunocompromised children aged 0.8–20.5 years | 40 | NPAG | WT, age, sex, creatinine clearance, ALT, AP | 2, with delayed absorption and nonlinear elimination | PO and IV | WT, age | WT, age | WT, age | NR | NR | NR | NR | NR | NR | [55] |
| Immunocompromised children aged 2–11 years | 35 | NON-MEM | WT, CYP2C19 genotype, ALT, AP | 2, with linear elimination | IV | WT | WT | WT | NR | NR | NR | NR | NR | NR | [61] |
| Patients undergoing HSCT aged <2 to 21 years | 59 | NON-MEM | WT, maturation function for voriconazole | 2-compartment model for voriconazole and 1-compartment for its metabolite, with linear voriconazole elimination but also nonlinear voriconazole elimination to its metabolite | Allometrically scaled bodyweight with a fixed exponent of 0.75 and normalized to 70 kg for both voriconazole and metabolite; maturation factor for voriconazole | Allometrically scaled bodyweight with a fixed exponent of 1 and normalized to 70 kg | Allometrically scaled bodyweight with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled bodyweight with a fixed exponent of 1 and normalized to 70 kg | Allometrically scaled bodyweight with a fixed exponent of 0.75 and normalized to 70 kg | NR | NR | NR | NR | NR | NR | [63] |

*ALB* albumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CF* cystic fibrosis, *CL* clearance, *CRP* C-reactive protein, *CYP* cytochrome P450, *F* bioavailability, *GGT* gamma-glutamyl transferase, *HSCT* hematopoietic stem cell transplantation, *HT* height, *IV* intravenous, *K* rate constant, *MD* multiple dose, *N* total patients or samples, *NON-MEM* nonlinear mixed effect modeling, *NPAG* non-parametric adaptive grid modeling, *NR* not reported, *PO* ‘per os’, *POS* powder for oral suspension, *Q1* intercompartmental clearance, *Q2* intercompartmental clearance, *SD* single dose, *V1* volume of distribution of the central compartment, *V2* volume of distribution of the peripheral compartment, *V3* volume of distribution of the peripheral compartment, *Vmax* maximum rate of enzyme activity, *WT* weight
undergoing HSCT were included in these studies. In two
studies, posaconazole was only administered as the mar-
keted oral suspension. The relative $F$ of posaconazole was
not determined in these studies [74, 75]. In the other study,
posaconazole was administered as a not yet marketed new
formulation, a powder for oral suspension (PFS), as well
as an intravenous solution [76]. The first NCA investigated
posaconazole orally as the marketed suspension at 6 or 9 mg/
kg in a two or three times-daily regimen in three different
age groups [74]. The second study used the marketed oral
posaconazole suspension as 120 mg/m$^2$ based on body
surface area (BSA) [75]. In the third study, posaconazole was
investigated as either an intravenous solution or as the new
oral PFS at 3.5 mg/kg, 4.5 mg/kg, or 6 mg/kg in a twice-
daily regimen on day 1, followed by the same dose in a once-
daily regimen in two different age groups [76].

Increasing the daily dose from 6 to 9 mg/kg or increasing
the dosing frequency of the marketed suspension from two
times daily to three times daily did not increase the expo-
sure of posaconazole. This suggests saturable absorption
in pediatric patients, which is also seen in adults. The authors
suggested that children aged >7 years showed higher expos-
ures compared with patients aged 2–7 years [74], imply-
ning that higher dosages are needed in younger patients to
achieve a comparable exposure to older patients. A dosing
regimen based on BSA resulted in a comparable mean expo-
sure as children aged 7–17 years on a 6-mg/kg twice-daily
regimen [75]. However, data based on BSA were not avail-
able for different age groups and exposure in the youngest
patients is therefore not exactly known with this approach.
Administering posaconazole intravenously or as a PFS in a
once-daily regimen (with a loading dose on day 1) resulted in
higher exposures compared with the exposures after a
twice-daily regimen of the marketed oral suspension in the
previously described report [74, 76]. Similarly to this earlier
report, posaconazole exposure was lower in younger patients
compared with older patients in all dosing groups [74, 76].
Furthermore, the exposure after oral PFS administration
was lower compared with intravenously administered posa-
conazole. As suggested by the authors, there seems to be
no bioequivalence between the intravenous and new PFS
formulations in pediatric patients [76].

7.2 Population Pharmacokinetic Analysis
of Posaconazole in Pediatric Patients

Currently, there are no population pharmacokinetic stud-
ies of posaconazole performed in neonates. One population
pharmacokinetic model was published in 117 immuno-
compromised infants, children, and adolescents aged 0.5–18
years. A detailed overview of the dosing regimens and
posaconazole pharmacokinetic results is shown in Table 13.
Posaconazole was administered as the marketed suspension
in the vast majority of these patients, with a mean daily
dose of 13.11 mg/kg [77]. A one-compartment model fitted
the data best. An overview of the pharmacokinetic model and
covariates tested is given in Table 10. Allometrically
scaled bodyweight was added on CL and $V_d$ and covari-
ates such as diarrhea and concomitant use of proton pump
inhibitors decreased posaconazole bioavailability only after
administration of the marketed suspension [77]. The phar-
cokinetic models and covariates tested are summarized in
Table 14.

The relative $K_{a}$ of the marketed suspension and tablets
was 0.197 h$^{-1}$ and 0.588 h$^{-1}$, respectively. The relative $F$
of the marketed suspension and tablets was not described. A
decrease of 33% in the relative $F$ of the marketed suspension
was seen in patients with diarrhea and a 42% decrease in
patients using proton pump inhibitors. As only the oral mar-
etked formulations were used, $V_d/F$ and apparent CL were
determined. Allometrically scaled bodyweight normalized
to 70 kg was added as covariate on posaconazole $V_d/F$ and
apparent CL [77].

7.3 Summary of Findings and Recommendations

Pediatric pharmacokinetic data of posaconazole are very
limited, and future research is particularly needed to explain
the PK of posaconazole in infants, and to further resolve its
PK in children and adolescents. Research topics should
include the $F$ of all the oral formulations and the PK in
critically ill patients and patients with CF. Furthermore, the
drug–drug interaction between posaconazole and CF trans-
membrane conductance regulator modulators might be an
interesting research topic. In adults, the gastro-resistant
tablets are the preferred formulation, but there are no phar-
cokinetic data of this formulation available in pediatric
patients. This oral tablet formulation urgently needs to be
studied in children and adolescents to confirm that this is
the most appropriate oral pharmaceutical formulation to be
used. For patients who are unable to swallow tablets, the new
PFS needs to be further explored. Other new child-friendly
formulations allowing the administration of smaller dosages
might be needed to further expand posaconazole treatment.

Although all studies administered posaconazole as an
oral formulation, the absolute and/or relative $F$ were not
described and need to be explored in pediatric patients.
Exposures after administration of the not yet marketed
posaconazole PFS were lower compared with intravenous
administration, and suggests that there is no bioequivalence.
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between these two formulations. Given the unknown \( F \) of the marketed formulations and the non-bioequivalence between intravenous and PFS formulations, dosing of posaconazole and switching between formulations should be accompanied by therapeutic drug monitoring.

The majority of available pediatric NCA only administered the suspension of posaconazole as an oral formulation. These data confirm adult observations that the marketed suspension shows saturable absorption. The new posaconazole PFS that is not yet on the market shows higher exposures in a once-daily regimen compared with the twice-daily regimen of the current marketed posaconazole suspension. After administration of both oral and intravenous formulations, posaconazole exposure seems lower in younger patients and higher dosages might be needed to reach the same exposure as older patients.

The population PK study included allometrically scaled bodyweight on CL and \( V_d \). Diarrhea and concomitant use of proton pump inhibitors were negatively associated with the relative \( F \) of the marketed posaconazole solution. Because of the high protein binding of posaconazole, it might be interesting to explore the influence of its unbound drug concentrations on posaconazole PK.

8 Isavuconazole

The relatively new triazole isavuconazole is not licensed for pediatric patients. The European Medicines Agency approved isavuconazole for adult patients in 2014 and the FDA approved isavuconazole in 2016 [7, 78]. Available formulations include an oral formulation as hard capsules and an intravenous formulation as powder for concentrate for solution. In adult patients, isavuconazole is indicated for the treatment of invasive aspergillosis. In addition, it is licensed for mucormycosis for patients who have a contraindication or intolerance for amphotericin B [7, 78]. Isavuconazole has not yet been approved for pediatric patients and the international guideline does not provide recommendations for dosing of isavuconazole in pediatric patients [1]. Dosing trials have been completed or are ongoing, thus more information is expected soon.

Isavuconazole is given as a pro-drug isavuconazonium sulfate. The oral \( F \) of isavuconazonium sulfate is 98% in adults [7]. After a rapid and complete absorption, isavuconazonium sulfate is quickly and completely cleaved to isavuconazole [7]. Oral and intravenous formulations can be used interchangeably. Food intake or fluctuations in pH do not influence the absorption of isavuconazole [79]. Based mostly on animal research, isavuconazole widely distributes in different tissues, including the liver, lungs, eyes, kidneys, skin, bone, nasal mucosa, and brain [80]. Isavuconazole is bound to plasma proteins for >99% and is metabolized by CYP3A4/A5 and uridine diphosphate glucuronosyltransferase (Table 1) [7].

To our current knowledge, there is only one pediatric study of isavuconazole available in the public domain outside of conference abstracts and case reports. This retrospective study included 29 patients with a hematological malignancy aged 3–18 years. In six patients, an 8-point sample curve was obtained over 12 h. The demographics and dosing regimens are not reported for these six patients separately. The median \( \text{AUC}_{0-12h} \) (range) in these six patients was 153.16 mg × h/L (86.31–169.45) [81]. Because of the small sample size and missing demographics and dosing information, it is difficult to draw any conclusions from these data.

8.1 Summary of Findings and Recommendations

Data on the PK of isavuconazole are urgently needed in pediatric patients including population pediatric PK data. Specifically for pediatric patients, information on \( F \) including information on dosing via a nasogastric tube are needed as well as information on bioequivalence after the intake of whole or opened capsules. As isavuconazole is highly protein bound, more research is needed on unbound drug concentrations in, for instance, the critically ill patient populations.

9 Conclusions

This review shows that the PK of fluconazole is extensively studied in the neonatal population and the PK of voriconazole is extensively studied in children and adolescents. Isavuconazole, itraconazole, and posaconazole are studied to a limited extent. Fluconazole data in children and adolescents are understated, while for other triazoles pharmacokinetic data in neonates and infants urgently need to be studied. Future studies should explore the PK of the newest triazole agents, understanding the \( F \) of the available formulations and learning more about interactions with food or administration over a nasogastric tube, the effect of CYP genotypes and other metabolic routes, the influence of other factors such as unbound drug concentrations for highly protein-bound agents, and the development and PK of new oral formulations that can easily be deployed in pediatric patients. In addition, information on the PK of triazoles in critically ill patient populations, the impact of dialysis, ECMO as well as renal or hepatic impairment is lacking in most cases and
Table 12  Non-compartmental analyses of posaconazole

| Population | Dose | Formulation | Weight | N  | SD, FD, or MD |
|------------|------|-------------|--------|----|---------------|
| Pediatric patients with hematological, non-hematological malignancies, or HSCT and neutropenia aged 3 months to <18 years | 7 to <18 years; 6 mg/kg PO every 12 h or 9 mg/kg PO every 12 h or 6 mg/kg every 8 h PO for 7–28 days | PO (suspension) | Median 29.8 kg | 136 | Day 1 FD 3 mo to < 2 years 6 mg/kg PO every 12 h or 9 mg/kg PO every 12 h or 6 mg/kg every 8 h PO for 7–28 days |
| | | | | | Value\(^a\) 103 ng/mL\(^b\) 196 ng/mL\(^b\) 175 ng/mL\(^b\) |
| | | | | | Arithmetic mean (%CV, STDV) 68.5 ng/mL\(^b\) 122 ng/mL\(^b\) 83.1, 101 |
| | | | | | Median (minimum-maximum) 3.38 h\(^b\) 5.01 h (2.92–11.60) |
| | | | | | Value\(^c\) 574 ng*/h/mL AUC\(_{0-12}\) 1200 ng*/h/mL 1210 ng*/h/mL |
| | | | | | Arithmetic mean (%CV, STDV) 1300 ng*/h/mL 76.9 |
| | | | | | Median (minimum-maximum) 7.95 h |
| | | | | | Value\(^d\) 1140 ng*/h/mL AUC\(_{0-12}\) 544 ng*/h/mL |
| | | | | | Arithmetic mean (%CV, STDV) 59.6 |
| | | | | | Median (minimum-maximum) 2.98–8.00 |
| | | | | | Value\(^e\) 424 ng*/h/mL AUC\(_{0-12}\) |
| | | | | | Arithmetic mean (%CV, STDV) 49.5 |
| | | | | | Median (minimum-maximum) 2.92–8.08 |

| Children with a hematological malignancies aged 2–13 years | 120 mg/m\(^2\) every 8 h | PO (suspension) | Mean (STDEV) 19.9 kg (0.1) | MD | Mean (STDEV)\(^a\) 960 ng/mL (6.30) |
|-------------------------------------------------------------|--------------------------|-------------------------|--------------------------|----|--------------------------|
| | | | | | Mean (STDEV)\(^a\) 860 ng/mL (5.80) |
| | | | | | Median (IQR)\(^a\) 15.9 Lh (9.95–27.86) |
| | | | | | Reference | 75 |
Table 12 (continued)

| Population | Dose | Formulation | Weight | N | SD, FD, or MD | Pharmacokinetic parameters | References |
|------------|------|-------------|--------|---|---------------|-----------------------------|------------|
| Hematology and oncology patients with documented or expected neutropenia aged 2–17 years | 3.5, 4.5, or 6.0 mg/kg IV every 12 h on day 1, followed by 3.5, 4.5, or 6.0 mg/kg (maximum 300 mg) once daily at days 2–10 and were switched to PFS in the same daily dose | PO (IV or powder for oral suspension) | NR | 118 | 2–6 years MD | C\text{max} | C | T\text{max} | AUC | T\text{1/2} | CL | V\text{d} | F |
| | 3.5 mg/kg (IV) | | | | | Geometric mean (%GCV) | Geometric mean (%GCV) | Median (minimum–maximum) | Geometric mean (%GCV) | NR | Geometric mean (%GCV) | | |
| | 4.5 mg/kg (IV) | | | | | 1590 ng/mL | 743 (55.0) | 1.78 h | 17800 ng*h/mL | | | | |
| | 4.5 mg/kg (IV) | | | | | 2320 ng/mL | 1300 (48.9) | (1.67–5.53) | 25600 ng*h/mL | | | | |
| | 4.5 mg/kg (PFS) | | | | | 1070 (30.0) | | | | | | | |
| | 6.0 mg/kg (IV) | | | | | 3060 ng/mL | 510 (36.0) | | | | | | |
| | 6.0 mg/kg (PFS) | | | | | 884 ng/mL | 960 (47.3) | | | | | | |
| | 1550 ng/mL | | | | | | | | | | | |
| | 1510 ng/mL | | | | | | | | | | | |
| | 7–17 years MD | 3.5 mg/kg (IV) | | | | Geometric mean (%GCV) | Geometric mean (%GCV) | Median (minimum–maximum) | Geometric mean (%GCV) | NR | Geometric mean (%GCV) | | |
| | 4.5 mg/kg (IV) | | | | | 2450 ng/mL | 1140 ng/mL | 1.77 h (0–3.5) | 27300 ng*h/mL | | | | |
| | 4.5 mg/kg (IV) | | | | | 2310 ng/mL | 1240 ng/mL | 1.75 h (1.52–1.80) | 29800 ng*h/mL | | | | |
| | 4.5 mg/kg (PFS) | | | | | 2310 ng/mL | | | | | | | |
| | 4.5 mg/kg (PFS) | | | | | 3340 ng/mL | 1930 ng/mL | 1.77 h (1.33–6.00) | 44200 ng*h/mL | | | | |
| | 3.5 mg/kg (PFS) | | | | | 3340 ng/mL | 1930 ng/mL | 1.77 h (1.33–6.00) | 44200 ng*h/mL | | | | |
| | 1340 ng/mL | | | | | | | | | | | |
| | 1370 ng/mL | | | | | | | | | | | |
| | 1670 ng/mL | | | | | | | | | | | |
| | 1200 ng/mL | | | | | | | | | | | |
| | 1400 ng/mL | | | | | | | | | | | |
| | 1785 ng/mL | | | | | | | | | | | |

AUC area under the curve, AUC\text{f} AUC from 0 to final quantifiable sample, BID twice daily, Cavg average serum concentration, CL clearance, C\text{max} maximum serum concentration in blood, CV coefficient of variation, F bioavailability, FD first dose, GCV geometric coefficient of variation, h hours, HSCT hematopoietic stem cell transplantation, IQR interquartile range, IV intravenous, MD multiple dose, N total patients, NR not reported, PFS powder for suspension, PO ‘per os’ (oral administration), SD single dose, SS steady state, STDV standard deviation, T\text{1/2} elimination half-life, TID three times daily, T\text{max} time to reach C\text{max}, V\text{d} volume of distribution

\(a\)Values recalculated/adjusted from original paper to create uniformity of units

\(b\)Values from one patient

\(c\)Unclear whether mean or median values are reported. Type of error was not mentioned
Table 13 Population pharmacokinetic estimates of posaconazole

| Population                          | Dose (range) | Formulation       | Weight (range) | N     | SD, FD or MD | Pharmacokinetic parameters | References |
|-------------------------------------|--------------|-------------------|----------------|-------|--------------|-----------------------------|------------|
| Immunocompromised children aged 5 months to 18 years | 13.11 mg/kg (2.67–48.95) | PO (tablet and suspension) | 117 MD | 17.8 kg (6.05–74.8) | AUC T¹/₂ CL V¹ \( K_a \) F \( f_D \) \( f_P \) | [77] |

\( AUC \) area under the curve, \( CL \) clearance, \( CL/F \) apparent clearance, \( F \) bioavailability, \( f_D \) fractional decrease of the bioavailability in patients with diarrhea (suspension), \( FD \) first dose, \( f_P \) fractional decrease of the bioavailability in patients using proton pump inhibitors (suspension), \( K_a \) rate of oral bioavailability, \( MD \) multiple dose, \( N \) total patients, \( NR \) not reported, \( PO \) ‘per os’, \( RSE \) relative standard error, \( SD \) single dose, \( T_{1/2} \) elimination half-life, \( V_d \) volume of distribution, \( V/F \) apparent volume of distribution.
### Table 14  Pharmacokinetic models of posaconazole

| Population | Subjects, N | Samples, N | Program | Covariates tested | Compartments | PO/IV | Covariates in final model | References |
|------------|-------------|------------|---------|-------------------|--------------|-------|--------------------------|------------|
| Immunocompromised children aged 5 months to 18 years | 117 | 338 | NONMEM | Diarrhea, treatment/ prophylaxis, macrolides, echinocandins, terbinafine, ciclosporin, tacrolimus, mycophenolate, rifamycins, carbamazepine, phenytoin, histamine H₂-receptor antagonists, proton pump inhibitors, or valaciclovir on bioavailability Macrolides, echinocandins, ciclosporin, tacrolimus, mycophenolate, rifampicin, carbamazepine, phenytoin, or valaciclovir on CL WT, sigmoidal maturation function based on PMA | l | PO | Allometrically scaled WT with a fixed exponent of 0.75 and normalized to 70 kg | Allometrically scaled WT with a fixed exponent of 1 and normalized to 70 kg | NR | Diarrhea, concurrent proton pump inhibitor administration | [77] |

*CL clearance, F bioavailability, IV intravenously, $K_{a}$ rate of oral bioavailability, N total, PMA postmenstrual age, PO ‘per os’, V volume of distribution*
should warrant further exploration. Better understanding of the PK is necessary for optimal clinical care and remaining knowledge gaps will need to be clarified.

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