Research Paper

# Risk assessment for extending the Biopharmaceutics Classification System-based biowaiver of immediate release dosage forms of fluconazole in adults to the paediatric population

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## Abstract

**Objectives** The paediatric population undergoes developmental changes in gastric pH, gastric emptying, intestinal transit time, membrane permeability, protein binding, body water, distribution and metabolism. It is widely recognised that changes in these parameters may result in an alteration of the plasma profile and thus in key bioequivalence parameters such as $C_{max}$ (maximum plasma concentration of drug) and area under the plasma concentration vs time profile curve. The aim of this work is to assess the risk of extending the biowaiver for immediate release dosage formulations of fluconazole from the adult to the paediatric population.

**Methods and key findings** Fluconazole exhibits good solubility and very rapid dissolution characteristics in various pH media. The absorption of fluconazole in children is known to be complete (over 90%) and not impaired by elevated pH, which is prevalent during the early days of life. Dose numbers calculated using body surface area are less than 1. Therefore, the risk to drug absorption due to differences in gastric pH, gastric emptying, intestinal transit, membrane permeability and metabolising enzymes between adults and children is considered low.

**Conclusions** Thus, it can be safely concluded that fluconazole meets highly soluble and highly permeable criteria in the paediatric population and can be allocated to class 1 of the Biopharmaceutics Classification System (BCS) for this population as well as in adults. Additionally, fluconazole has an excellent safety profile in children, similar to that in adults. The BCS-based biowaiver claimed in adults can be safely extended to the paediatric population provided that the requirements in excipient selection and dissolution profile comparison using BCS-based dissolution conditions as stated in the biowaiver monograph for fluconazole immediate release dosage forms in adults are fulfilled.

## Introduction

In the absence of sufficient clinical data in the paediatric population, owing to technical and ethical reasons, adult clinical data are commonly applied to predict pharmacokinetic and pharmacodynamic responses in children.[1] However, these predictions are often based on weight or age rather than taking all covariates into account. The paediatric population undergoes rapid developmental changes in anatomy and physiology. Some examples include the evolution of kidney and liver functions as well as the expression and function of receptors and proteins.[2]

The developmental changes in target receptor/tissue expression are essentially non-linear and exhibit variation among organs as well as among the different pathways and receptors, resulting in variation in pharmacodynamic response to a drug candidate between children and adult population and even within the diverse paediatric

population group. Similarly, differences in absorption, distribution, metabolism and excretion may arise due to the variation in gastric pH, gastric emptying, intestinal transit, body water, fat, concentration of binding proteins and their affinity to drug molecules, metabolising enzyme maturation and capacity, and renal function. Besides these factors, establishing a dosing regimen in the paediatric population should also consider intra- and interindividual variability arising from genetic-, environmental- and disease-related factors and drug interactions. Therefore, dosing children simply based on for example body weight in milligram per kilogram may expose them to over- or underdosing.[2] Recognising these challenges, regulatory bodies have initiated various programs to promote research in the paediatric population,[3–10] and the importance of understanding the pharmacokinetic and pharmacodynamic relationship of the drug for establishing an appropriate dosing regimen in the paediatric population group cannot be over emphasised.[3–10]

With respect to approval of generic versions of drug products, various options, including pharmacokinetic bioequivalence studies and the biowaiver procedure are currently available.[11–13] At present, biowaiver decisions for drug products, irrespective of the age for which medication is indicated, are primarily based on the physicochemical and pharmacokinetic properties of drug substances pertaining to the adult population. The biowaiver is often extended to the paediatric population group without further consideration being given to the anatomical and physiological differences exhibited by this group, which may promulgate differences in absorption, distribution, metabolism and excretion of the drug substance.[10] Yet, it may be important to consider precisely these dissimilarities when extending BCS (Biopharmaceutics Classification System)-based biowaiver concepts to products designed for the paediatric population.

Fluconazole, an orally active bis-triazole derivative, is indicated for the treatment of oropharyngeal candidiasis, *Candida* esophagitis or systemic *Candida* infections in children.[14–18] In immunocompromised patients, it is used for both prophylaxis and treatment of superficial and systemic fungal infections, mainly invasive candidiasis, candidemia and cryptococcal meningitis.[14–18] Additionally, favourable pharmacokinetic properties make it a primary therapeutic drug candidate in the treatment of candidemia infections, mucocutaneous candidiasis and genital candidiasis in both children and adult population groups.[14,19] Further, its effectiveness in the treatment of systemic fungal infections, mainly candidemia infections, was shown to be similar between paediatric and adult groups.

Recently, a biowaiver monograph for immediate release dosage forms of fluconazole, based on its biopharma-

ceutical and clinical properties in the adult population has been published.[20] The aim of the current work was to evaluate the feasibility of extending the biowaiver for oral fluconazole products from adult to paediatric dosing situations by linking the information in the biowaiver monograph to the physiological characteristics of children.

## Materials and Methods

### Literature search

A literature search was performed in PubMed, Micromedex and Web of Science databases up to March 2014. Information was also retrieved from the World Health Organization (WHO),[11] US FDA[12] and European Medicines Agency (EMA)[13] guidance documents. Key words used for the search were fluconazole, BCS, solubility, paediatric indications, absorption, distribution, metabolism, elimination, gastric emptying, intestinal transit, toxicity and paediatric population.

### Solubility classification for application in the paediatric population

The solubility data of fluconazole were obtained from the literature as well as from experimental studies performed at LaGray Chemical Co, Ghana, and reported in the recently published fluconazole biowaiver monograph.[20]

Rather than basing the solubility classification on the BCS, a paediatric dose number (Do) was calculated by using the following equation:[21]

$$Do = \frac{(Paediatric\ dose)/(Paediatric\ reference\ volume)}{Drug\ solubility}$$

Reference volumes for paediatric groups were determined by three methods:

Method 1:[22] In 2012, the Best Pharmaceuticals for Children Act – Pediatric Biopharmaceutics Classification System working group published a workshop report proposing a paediatric reference volume of 25 ml. However, the basis for proposing this volume was not provided.[22]

Method 2:[21] Reference volumes were determined for paediatric groups relative to the adult volume of 250 ml and body surface area of 1.73 m², which was calculated using 50 percentile values for boys,[21] provided by the Centers for Disease Control and Prevention growth charts,[23,24] for weight and height using the following equation:

$$Paediatric\ reference\ volume\ (ml)$$
$$= \frac{Pediatric\ body\ surface\ area\ (m^2) \times 250}{1.73}$$

Method 3:[25–27]

$$\text{Paediatric reference volume (ml)} = \frac{\text{Weight (kg)} \times 0.56}{40} \times 250$$

where 0.56 ml/kg and 40 ml are estimates of the gastric fluid volumes in children[25] and adults,[26] respectively, in the fasted state, and 250 ml is the reference volume used in the adult BCS.[11–13]

## Dissolution data

Dissolution data of Diflucan capsules in different pH media were also taken from the recently published fluconazole biowaiver monograph.[20] Dissolution studies were performed using basket apparatus (Disso 2000; Lab India Instruments Pvt Ltd, Mumbai, India), run at 100 rpm in 900-ml medium (0.1N HCl, acetate buffer of pH 4.5 and phosphate buffer of pH 6.8) maintained at 37 ± 0.5°C.[20]

## Risk assessment

Physiological parameters including gastrointestinal pH, gastric emptying, intestinal transit time, membrane permeability, protein binding, body water, distribution and metabolism are known to influence drug absorption and/or the plasma profile and hence were considered here as additional risk factors to the bioequivalence of drug products. The variability of these parameters within the paediatric population and in comparison with adults was reviewed, and parameters were classified into black, dark gray and light gray zones depending on the relative risk of each attribute. The parameters marked in black are considered to be high-risk factors to drug absorption by virtue of evidence available from the literature showing that they differ considerably between paediatric and adult populations. Medium risks, marked in dark gray, represent the transition phase in development during which attributes approach to adult values, whereby such attributes may still pose some risk with respect to similarity of drug absorption. Low risk attributes, represented by light gray zones, are those attributes with values similar to those in the adult population and which are unlikely to cause variation in drug absorption.

## General Characteristics

### Therapeutic indications and dose

Fluconazole is indicated in children for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of *Candida* infections in immunocompromised patients.[14–19,28,29] Pharmacokinetic studies have established dose proportionality between children and adults.[14–19,28,29]

**Table 1** Fluconazole adult dose and the corresponding paediatric dose that produces equal exposure

| Dose in paediatric patients (mg/kg)[a] | Dose in adults (mg) |
| --- | --- |
| 3 | 100 |
| 6 | 200 |
| 12 | 400 |

[a]Older children showing similar clearance to adults should not be given a dose exceeding 600 mg/day.

In infants, toddlers and children (from 28 days old to 11 years old), mucosal candidiasis is treated with an initial dose of 6 mg/kg followed by a daily dose of 3 mg/kg. Invasive candidiasis and cryptococcal meningitis is treated with a daily dose of 6–12 mg/kg. As a prophylaxis measure to prevent *Candida* infection in immunocompromised patients, 3–12 mg/kg is recommended.[15,18]

For term newborn infants between 0 and 14 days old, the same dose as recommended for infants, toddlers and children should be given every 72 h. In infants between 15 and 27 days old, the dosing frequency must be reduced to 48 h.[15,18]

The weight and pubertal development must be considered in adolescents (12–17 years old)[15,18] to determine a suitable dose (adult or child dose). The clearance of fluconazole in younger children is higher; therefore, higher milligram per kilogram doses than in adults are recommended for similar indications in those groups. Consequently, the comparative adult vs paediatric dose equivalency, shown in Table 1, can be used as a guide in dose selection for a paediatric group to achieve similar exposure.[15,18] The maximum loading dose allowed is 800 mg for adults (equivalent to 12 mg/kg assuming an average adult weighing 65 kg) in case of severe invasive candidiasis, whereas, the maximum loading dose for older children showing similar clearance to adults is 600 mg for the same indication.[15,18]

The availability of fluconazole in tablets, capsules, powder for oral suspensions and intravenous infusion dosage forms is in concordance with the administration of liquids to younger children and tablets/capsules to older children. Bioequivalence has been established between 100 mg tablets and two strengths of suspension formulations (50 mg/5 ml and 200 mg/5 ml), when administered as a single 200-mg dose.[15,18]

## Pharmacokinetics of fluconazole in the paediatric population

Area under the curve (AUC) values after administration of fluconazole 2–8 mg/kg to paediatric patients (9 months–15 years) can be described as approximately 38 μg/h per millilitre per 1 mg/kg dose unit. The average plasma elimination half-life after a single dose was 24 h, whereas after multiple

dosing, the average plasma elimination half-life was 15–18 h with a volume of distribution of 0.88 l/kg.[15,18]

Brammer and Coates studied the pharmacokinetics of fluconazole in 101 paediatric patients who were categorised by age into 3 months–2 years; 2–12 years and 12–16 years. The volume of distribution of 1.18–2.25 l/kg was highest among neonatal patients, whereas, the value in young adults approached the adult average value of 0.7 l/kg.[30] In comparison with adults, the fluconazole clearance was slow in neonates, whereas it was more rapid in other paediatric groups. At the same time, the volume of distribution was higher and more variable in neonates than infants, indicating the need for increasing the dose, but dosing less frequently in neonates.[30]

Similar results were recorded in a later study in which fluconazole 6 mg/kg dose was administered intravenously every 72 h, for a maximum of 5 doses, during the first 2 weeks of life to 12 premature infants in an open phase I–II clinical study. The volume of distribution and clearance increased from 1.18 l/kg and 0.18 ml/min per kilogram at birth to 2.25 l/kg and 0.52 ml/min per kilogram, respectively, by 2 weeks of age, whereas half-life values decreased to 55.2 h from 88.6 h, indicating that the 72-h dosing frequency in the first 2 weeks of life should be reduced to 48 h during the next 2 weeks of life.[31]

Nahata *et al.* compared the blood concentrations of fluconazole after oral and intravenous (i.v.) administration of 6 mg/kg in 6 premature infants (median gestational age of 30 weeks). Four patients were administered oral fluconazole only, whereas, two further patients received both an oral and an i.v. dose with the two treatments separated by at least 1 week. The $C_{max}$, AUC and clearance achieved after oral administration were 6.0–13.3 µg/ml, 340.7–636.1 µg/h per millilitre and 0.16–0.29 ml/min per kilogram, respectively.[32] The $C_{max}$ and AUC ranged from 9.99–13.5 µg/ml to 340.8–425.3 µg/h per millilitre, respectively, in the two patients who had received an i.v. dose. The systemic exposure of fluconazole with respect to $C_{max}$ (maximum serum concentration) and AUC via oral and i.v. routes in these two patients were comparable.[32]

Wenzl *et al.* reported somewhat lower serum concentrations of fluconazole in another group of premature neonates (mean gestational age of 27 weeks) who were treated orally with 4.5–6 mg/kg per day for *Candida albicans* septicaemia infection. They reported AUC values of 131.2–233.0 µg/h per millilitre, volumes of distribution of 1.21–1.88 l/kg and $C_{max}$ values of 6.8–11.9 µg/ml. Despite the somewhat lower serum concentrations, almost all the patients were clinically cured. Only one patient, dosed 4 mg/kg, showed relapse and subtherapeutic serum levels (3.2 µg/ml), indicating the need for a higher dose.[33] After dosage was adjusted to 6 mg/kg per day, serum levels (7.4 µg/ml) were within the therapeutic range (5–15 µg/ml)

and subsequent follow up demonstrated microbiological and clinical cure.[33]

In a study of immunocompromised children (age 1–15 years) with leukaemia, administered fluconazole (6 mg/kg) intravenously followed by seven oral doses of 3 mg/kg, an oral bioavailability of 92% was reported along with a volume of distribution of 0.77 l/kg.[34]

### Therapeutic index and toxicity

Safety of fluconazole, a wide therapeutic index drug, in children has been demonstrated in several studies.[16,28,35,36] It is tolerated well by both adults and children.[10–15,27–30,37] In fact, the safety profile of fluconazole in children mirrors the safety profile of fluconazole in adults.[38–41] In one study, only 0.5% of children showed liver-related side effects, and in those children, the symptoms resolved during continued treatment. In the same study, less than 5% of patients showed transient increases in liver enzymes.[38]

Egunsola *et al.* performed a retrospective safety assessment of fluconazole in paediatric patients by surveying 90 articles published in 1986–2011, reporting a total of 4209 patients. Out of 794 adverse effects recorded in 35 studies, hepatotoxicity was the main adverse event, accounting for 47.6% of all adverse effects.[42] Gastrointestinal events constituted the second most common adverse effect. Other adverse effects noted included renal dysfunction, haemotological abnormalities and rash. However, the relative risk of all the adverse effects was statistically insignificant in comparison with placebo.[42] The 41 drug withdrawals reported were mainly due to problems with liver function, with elevated liver enzymes being the cause of 42% of these withdrawals. Symptoms of hepatotoxicity were resolved in 84% of the patients in whom follow up was completed. A drug interaction was documented in five reports. Of these five drug interactions, two drug interactions were recorded in children with all-trans retinoic acid, which resulted in acute renal failure and pseudotumour cerebri. Renal failure following interaction with tacrolimus in a 9-year-old child was also reported. The two other drug interactions occurred as a consequence of fluconazole's co-administration with amitriptyline (syncope in 12-year-old child) and vincristine (severe constipation). Therefore, concomitant use with other medications must be carefully considered. Overall, fluconazole was concluded to be safe in children.[42]

Another safety consideration is the extrapolation of the use of loading doses in adults to children. An AUC/minimum inhibitory concentration (MIC) index of >50, with the MIC breakpoint typically at 8 µg/ml or less, is considered critical to successful management of life-threatening fungal infections.[14,43,44] To achieve this index, an AUC of 400 µg/h per millilitre should be targeted. In infants,

12 mg/kg per day dose is believed to reach the target AUC of $\geq 400\ \mu g/h$ per millilitre.[45,46] Due to fluconazole's prolonged half-life in infants, it may take 5–7 days to achieve the desired target drug exposure.[46,47]

Pipier *et al.* performed a prospective, single-centre, open-label pharmacokinetics and safety, clinical study of fluconazole loading dose in infants (<60 days old) to determine if the adult loading dose (1600 mg, approximately 25 mg/kg) would achieve the therapeutic target drug concentration when administered to infants.[47] Fluconazole was administered intravenously as an infusion of 25 mg/kg over 1 h on day 1, followed by maintenance doses of 12 mg/kg per day, also infused over a period of 1 h on days 2–5. The target concentration of $AUC_{0-24} > 400\ \mu g/h$ per millilitre was achieved in 5 out of 8 patients after a single dose of 25 mg/kg was administered. A trough concentration of more than $8\ \mu g/ml$ was achieved in all the patients. The loading dose was well tolerated with 25% patients (2 patients) experiencing an adverse effect, although these were concluded to be related to the underlying disease state.[47] One infant who developed ventricular tachycardia had a previous history of complex congenital heart disease and arrhythmias, whereas, a transiently worsening renal insufficiency in another infant was believed to be secondary to his clinical condition and extracorporeal membrane oxygenation support. No hepatotoxicity or elevation in liver transaminases was observed.[47]

## Discussion

An overview of the likelihood of various physiological parameters to present a risk to drug absorption/bio-equivalence in children *vis à vis* adults is portrayed in Table 2. The risk factors considered in this assessment are in line with Batchelor *et al.*[48]

### Gastric pH

At birth, the gastric pH varies from 6 to 8, and within a few hours, the value dips to 1–3. By the 10th day, it has reverted to pH 6–8. Subsequently, the pH starts to decline again, so that after 1 year, it has reached a value of 1–2, and by the age of 3 years, has attained the adult value of pH 1–3.5.[49] The higher pH immediately after birth is due to a combination of alkaline amniotic fluid with low basal acid output and a low volume of gastric secretions.[50] One report indicated carbohydrate metabolism instability as a possible cause, but no statistically significant correlation was apparent with pH fluctuation.[51] Higher glucagon levels observed in neonates on day 4 of life were suggested to serve as a pretext for a higher pH due to its inhibitory effect on gastrin-mediated gastric acid secretion effect, in spite of high blood levels of gastrin.[52]

**Table 2**   Risk factors to drug absorption

| Physiological parameters | Infants (0–12 months) | | | | | | Toddlers (1–3 years old) | Children (4–6 years old) | Children (7–12 years old) | Adolescents (13–18 years) | Adults |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Birth | 24–48 h | 10th–30th day | 3 months | 6 months | 1 year | | | | | |
| Gastric pH | 6–8 | 1–3 | 6–8 | – | – | – | 1–3.5 | 1–3.5 | 1–3.5 | 1–3.5 | 1–3.5 |
| Gastric emptying | Slow and linear | Similar to adults | | | | | | | | | |
| Intestinal transit | Fast | | | | | | | | | | |
| Bile salt pool | Fat soluble drugs poorly absorbed | | | | – | – | – | – | – | – | – |
| Membrane permeability | Intestinal permeability BBB high permeability | | | – | – | – | – | – | – | – | – |
| Protein binding | Unbound drug high | | | | | 60% | 60% | | | | |
| Body water | 70–75% water soluble drugs high distribution | | | | | | 60% | 60% | 60% | 60% | 60% |
| Hepatic enzyme activity | Lower than in adults | | | | | | – | – | – | – | – |
| Microsomal enzymatic system | Higher than in adults | | | | | | – | – | – | – | – |

High risk ■   Medium risk ▨   Low risk ▢

The greatest divergence in pH from adult values are seen immediately after birth and post 10 days; therefore, these groups are likely to show the maximum difference in absorption in comparison with adults for drugs whose absorption is affected by pH. For this reason, the pH in these groups has been marked as a high risk factor in Table 2. From 3 months of age, the values start to recede until the age of 2–3 years, when the adult values are attained. Before the age of 1 year, the pH value may still be on the higher side, and thus represents a medium risk to the drug absorption. The variation in pH occurring during the early years manifests in differences in the absorption of many drugs. For example, acid labile drugs are often absorbed better in this age group than in older children or adults.[53–56]

Another factor worthy of note here is the age effect on gastric lipase (GL) secretion in the stomach. Secretion of GL starts 13 weeks postconception, albeit in lower levels throughout infancy. As in adults, GL in children assumes importance in the initial digestion of short and medium chain fatty acids. It is more effective at alkaline pH and aids in digestion by emulsification process.[57,58] The assimilation of drugs given in drops containing oily vehicles may therefore be affected by the age of the child due to changing pH, which in turn may result in variation in enzyme efficiency.

Fluconazole is slightly lipophilic,[59,60] but exhibits good solubility characteristics across a wide pH range, 1.2–7.4.[61,62] This is also supported by the complete dissolution of the drug in different pH media.[20] Further, it is reported that the absorption of fluconazole is not impaired by increased pH.[63,64] In light of this evidence, the pH changes seen during early childhood are not expected to present a risk to fluconazole absorption from suspension formulations, which constitute the usual dosage form administered to younger children.

## Gastric emptying and intestinal transit

The primary site of drug absorption is the small intestine; therefore, it is likely that slower gastric emptying will decrease the absorption rate of drugs.[65–67] Gastric emptying rate of solid immediate release dosage forms in adults after fasted state administration is dependent on the phase of the migrating myoelectrical complex cycle (MMCC) at the time of administration as well as the volume of liquids ingested, and it is usually assumed to be a first-order kinetic process with a half-life of about 15 min.[68–70] On the other hand, in the fed state, MMCC is replaced by a zero-order kinetic process, depending on composition, size and temperature of the meal, as well as the timing of administering the solid dosage form in relation to the meal.[70,71]

In pre-term infants, gastric emptying of milk was demonstrated to be linear, with a mean half, emptying times between 36 and 72 min.[72] It has been reported that gastric-

emptying rates after birth reaches to adult values by the age of 3–8 months.[73] In the fasted state, gastric-emptying rates are comparable in terms of infants and maturing infants.[22,74]

Generally, it could be expected that the shorter intestinal residence times in children may result in incomplete absorption of some drugs, especially when formulated as controlled release dosage forms.[75] Intestinal residence time is directly influenced by the length of the small intestine.[22] Weaver *et al.* collected data from 8 published reports of necropsy measurement of 1010 guts and determined mean small intestinal length to be 275 cm at term, 380 cm at 1 year, 450 cm at 5 years, 500 cm at 10 years and 575 cm at 20 years.[76] The growth rate of the small intestines is rapid in infancy and subsequently grows in direct proportion to the body length. Disease states, especially diarrhoea, which is more prevalent in children, also affect transit times.[22,77]

In adults, fluconazole peak and extent of exposure were not affected by co-administration of a heavy breakfast; however, in line with the observation of a significant prolongation of gastric-emptying times, $T_{max}$ was delayed by approximately 2 h.[78] Given that gastric emptying is slower in infants, it seems reasonable to expect a delayed $T_{max}$, similar to that observed in adults dosed in the fed state. However, as the summary of product characteristics (SmPC) for Diflucan recommends administrating fluconazole with or without food, it seems safe to assume that such a potential delay would not be clinically relevant.[15,18] Moreover, because there is a lack of food effect on drug absorption in adults after taking fluconazole with a high-fat meal, it seems unlikely that liquid, semisolid and low-density food in children would affect fluconazole peak and extent of exposure.[78,79]

Also, given that similar serum concentrations were observed in adults and children,[15,18,27,38,80] after correcting the dose for the latter due to differences in Cl and Vd, it seems safe to conclude that the fluconazole mean absorption time is still faster than the shorter mean intestinal residence time observed in infants.

## Clearance, volume of distribution and protein binding

The pharmacokinetics of fluconazole between young (≤3 years) and older children (>3 years) are similar and independent of gender.[14,15,18,30–34,37]

Fluconazole is eliminated rapidly in children (except in neonates) and exhibits a higher volume of distribution, possibly due to low fat tissue and high extracellular and total body water in neonates and infants.[81,82] Consequently, it is accumulated less on multiple dosing and steady-state levels are attained faster than in adults.[14,15,18,30–34,37] Therefore, higher doses of 6–12 mg/kg per day are recommended in

severe, life-threatening infections to achieve a comparable therapeutic outcome.[14,15,18,30–34,37] Further, due to its low protein binding, fluconazole is able to penetrate body fluids.[14–18]

The volume of distribution and half-life at the end of a 7-day therapy was 0.84 l/kg and 18.1 h, respectively, after administration of 1, 4 or 8 mg/kg per day of fluconazole for 7 days to 26 children with neoplastic diseases (aged between 5 and 15 years) for prophylactic purposes.[37] In another study in 10 immunocompromised children with leukaemia or aplastic anaemia (aged 1–15 years), fluconazole, when administered as a single i.v. dose of 6 mg/kg and then seven oral 3 mg/kg doses, produced an oral bioavailability of 92%, a clearance of 0.63 ml/min per kilogram and an elimination half-life of 15.6 h.[34] Slightly longer elimination half-lives (19.8–42.3 h) have been reported in children with HIV infections receiving single oral doses of 2 or 8 mg/kg.[83] In yet another study, elimination in premature infants of mean gestational age of 27.4 weeks and mean birth weight of 912 g was slower with a mean elimination half-life of 88.6 h at birth, 67.5 h approximately 1 week later and 55.2 h approximately 2 weeks after birth.[31]

Generally, renal function is reduced in infants, and adult values are reached in 6–12 months.[66,84,85] Similarly, tubular secretion is immature at birth and reaches adult capacity during the first year of life.[50] Changes in renal function can significantly affect plasma levels of drugs that are mainly eliminated by this route, like fluconazole. Failure to account for the ontogeny of renal function to adjust fluconazole dosing might expose children to excessively high concentrations. The immature renal elimination system may cause drug accumulation warranting less frequent dosing intervals.[75,78,84,85]

The major metabolites of fluconazole detected in urine of adult healthy volunteers were fluconazole glucuronide conjugate (6.5%) and fluconazole N-oxide (2.0%).[86] Fluconazole is primarily excreted via the renal route with over than 80% of the dose excreted unchanged in urine in adults, whereas, in children approximately 65% is excreted unchanged in urine.[14,15,18,37] These results taken together with the higher total body clearance observed in children[34] suggest that metabolic capacity, especially, glucuronidation capacity might be higher in the paediatric population. Higher glucuronidation capacity after the neonatal stage is also reported for morphine.[87]

In the paediatric population, the concentration of binding proteins, their binding capacity and affinity towards drug molecules is low.[50,88] Consequently, drugs exhibiting high protein binding may show remarkable differences in pharmacokinetic properties between paediatric and adult population. However, in the case of fluconazole, the plasma protein binding in adults is already low (11–12%) and clinically insignificant,[14,15,18] although binding to

proteins does increase (23%) in chronic renal failure adult patients.[89] Nevertheless, risks associated with changes in protein binding do not generally impact drug absorption, and specifically, the risk of an effect on fluconazole absorption is minimal (Table 3).

## Metabolism

Liver volume (LV) is an important variable when predicting hepatic drug clearance.[90] Although some authors recommend using equations based on body surface area to predict paediatric LV and consequently paediatric clearance,[90] it is important to highlight that such a scaling approach might lead to under- or overpredicted values because the body surface area is not a good descriptor of metabolic function.[91,92]

Generally, the metabolic degradation system is relatively immature mainly in younger infants, which may translate into higher drug half-life and slower drug clearance from systemic circulation.[81] Together with low first pass metabolism in children, higher blood levels are attained for many drugs.[93,94] However, in the case of fluconazole, the elimination half-life in children (15–25 h) is shorter than in adults (30 h) and total body clearance is higher in children (0.63 ml/min per kilogram)[34] in comparison with adults (0.27 ml/min per kilogram), suggesting higher metabolic activity and more efficient elimination of fluconazole in the paediatric population.[15,18]

## Permeability

More than 90% drug is absorbed after oral administration in children aged 1–15 years,[34] confirming that this paediatric population exhibits a high permeability, equivalent to that observed in adults,[20] as has been theoretically anticipated by some authors.[27] Furthermore, the extent of exposure ($AUC_{0\text{-}inf}$) by oral and i.v. routes has been found to be similar even in preterm infants,[32] so it seems safe to conclude that fluconazole can be classified as a highly permeable drug across all paediatric populations.

## Solubility

The solubility values reported at 37°C were 8.03, 6.91, 7.82 and 6.90 mg/ml in 0.1 N HCl, acetate buffer of pH 4.5, phosphate buffer of pH 6.8 and pH 7.4, respectively.[20,61,62]

The solubility of the active pharmaceutical ingredient (API) is one of three essential components of the BCS-based biowaiver. For adults, drugs are classified as 'highly soluble' if highest dose strength dissolves in 250 ml of water.[11–13] The use of 250-ml volume in solubility definition emanates from the fact that dosage forms are administered to adults with a glass of water, which is approximately 250 ml, in bioequivalence studies.

**Table 3** Risk assessment for fluconazole absorption

| Physiological parameters | Infants (0–12 months) Birth / 24–48 h / 10th–30th day / 3 months / 6 months / 1 year | Toddlers (1–3 years old) | Children (4–6 years old) | Children (7–12 years old) | Adolescents (13–18 years) | References |
|---|---|---|---|---|---|---|
| Gastric pH | ❖ Absorption of fluconazole is not impaired by increased pH. | | | | | [62,63] |
| Gastric emptying | ❖ SmPC for Diflucan recommends administrating fluconazole with or without food. | | | | | [15,18,27,38,77–79] |
| Intestinal transit | ❖ Similar serum concentrations were observed in adults and children. | | | | | [15,18,27,38,77–79] |
| Membrane permeability | ❖ More than 90% drug is absorbed after oral administration in children aged 1–15 years. ❖ Children exhibit permeability equivalent to the adults | | | | | [14,15,18,20,27,36,74] |
| Protein binding | ❖ Plasma protein binding is low and clinically insignificant. | | | | | [14,15,18] |
| Body water | ❖ Higher volume of distribution in children; however, corrected doses produce equal exposure in children and adults. ❖ It is accumulated less in children on multiple dosing and steady-state levels are attained faster than adults. | | | | | [14,15,18,30–34,37] |
| Hepatic enzyme activity | ❖ Poorly metabolised drug. ❖ Approximately 65% of the dose is excreted unchanged in urine compared with over 80% in adults. | | | | | [14,15,18,37] |
| Microsomal enzymatic system | ❖ Metabolic capacity, especially, glucuronidation capacity might be higher in paediatric population. ❖ More efficient elimination of fluconazole in the paediatric population. | | | | | |
| Solubility | ❖ Solubility of 8.03, 6.91, 7.82 and 6.90 mg/ml in 0.1 N HCl, acetate buffer of pH 4.5, phosphate buffer of pH 6.8 and pH 7.4, respectively. ❖ Fluconazole can be classified as Biopharmaceutics Classification System Class 1 drug even after considering the details of paediatric physiology | | | | | [20,60,61] |

SmPC, summary of product characteristics. ▨ Light grey colour shows low risk to fluconazole absorption.

When the paediatric reference volume of 25 ml is considered, according to Method 1, the definition of high solubility is not met by the paediatric subgroups for fluconazole. However, the proposed volume appears too conservative, especially for infants older than 6 months, as no consideration is given to the age, body weight and height, and no scientific base for supporting such a volume has been put forward.

As an alternative, Gandhi *et al.* used body surface area to calculate the paediatric reference volume taking into consideration an adult reference volume of 250 ml and body surface area of 1.73 m² in pursuit of BCS paediatric classification for five drug candidates.[21] Using this approach for fluconazole as stated in Method 2, the dose numbers, irrespective of maximum strength or maximum recommended daily dose, or even highest off-loading dose, 25 mg/kg (results not shown here), for each paediatric population subgroup are less than 1 (Tables 4–6). Thus, fluconazole would be classified as BCS Class 1, according to WHO/US-FDA and EMA guidelines, in the paediatric population when reference volumes derived from the body surface area are considered.

Although this body surface area approach seems to be quite interesting, children are not simply 'smaller-area adults'. Growth, especially during the first 10 years of life, is not linear.[94] Complicating it further is a higher surface area to weight ratio in infants and young children as compared with older children and young adults.[95]

The reference volumes calculated by Method 3 use reported gastric fluid volumes of 0.56 ml/kg and 40 ml in children and adults, respectively.[25,26] The reference volumes obtained by this Method 3 are lower than the Method 2 (Table 4). Except for younger children (4–6 years old), dose numbers are less than 1 when the maximum dose recommended by SmPC is considered (Table 5). The dose numbers of greater than 1, using Method 3, for children (4–6 years old) might be an overly conservative estimate, as doses as high as 600 mg (equivalent to 32 mg/kg, considering the average weight for this group) are prescribed only to older children showing similar clearance to adults.

The dose numbers are also less than 1 (except for the dose numbers for infants <6 months old, calculated using Method 3) when a maximum dose strength of 200 mg is considered (Table 6). Noting that it is unlikely that infants will be administered a dose as high as 200 mg (this would be equivalent to a range from 55 to 22 mg/kg, considering infant weights), fluconazole can be classified as BCS Class 1 drug even after considering the details of paediatric physiology.

Fluconazole is absorbed almost completely (>90%) and dose numbers, when taking age-appropriate dosing into consideration, are generally less than 1. Therefore, it seems safe to conclude that fluconazole meets highly soluble and

**Table 4** Estimated dose and reference volume of fluconazole in the paediatric population

| Parameter | Postconception (≤1 week) | Infants (0–6 months) | Infants (6–12 months) | Toddlers (1–3 years old) | Children (4–6 years old) | Children (7–12 years old) | Adolescents (13–18 years) |
|---|---|---|---|---|---|---|---|
| Dose[a] | 12 mg/kg | 12 mg/kg | 12 mg/kg | 12 mg/kg | 600 mg | 600 mg | 600 mg |
| Weight (kg)[b] | 3.6 | 3.6–7.8 | 7.8–10.4 | 10.4–14.3 | 16–21 | 23–40.5 | 45.5–67 |
| Average weight (kg) | 3.6 | 5.7 | 9.1 | 12.35 | 18.5 | 31.75 | 56.25 |
| Dose (mg) | 43.2 | 68.4 | 109.2 | 148.2 | 600[a] | 600[a] | 600[a] |
| Height (cm)[b] | 50.0 | 50–67 | 67–75.5 | 75.5–96 | 102–116 | 122–149 | 156–176 |
| Average height (cm)[b] | 50.0 | 58.5 | 71.25 | 85.75 | 109 | 135.5 | 166 |
| Volume (ml) (Method 1) | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Volume (ml) (Method 2) | 32.313 | 43.980 | 61.328 | 78.378 | 108.154 | 157.974 | 232.733 |
| Volume (ml) (Method 3) | 12.6 | 19.95 | 31.85 | 43.23 | 64.75 | 111.13 | 196.88 |

[a]Children with clearance similar to adults – total dose per day should not exceed 600 mg. [b]50 percentile of values for boys in Centers for Disease Control and Prevention growth charts.

**Table 5** Dose numbers calculated from experimentally determined saturation solubility values of fluconazole in various buffered media, maintained at 37°C, using the maximum dose recommended in the SmPC

| Medium | Postconception (≤1 week) | Infants (0–6 months) | Infants (6–12 months) | Toddlers (1–3 years old) | Children (4–6 years old) | Children (7–12 years old) | Adolescents (13–18 years) |
|---|---|---|---|---|---|---|---|
| Dose numbers (Method 1)[a] | | | | | | | |
| 0.1 N HCl | 0.215 | 0.341 | 0.544 | 0.738 | **2.989** | **2.989** | **2.989** |
| Acetate buffer (pH 4.5) | 0.250 | 0.396 | 0.632 | 0.858 | **3.473** | **3.473** | **3.473** |
| Phosphate buffer (pH 6.8) | 0.221 | 0.350 | 0.559 | 0.758 | **3.069** | **3.069** | **3.069** |
| Dose numbers (Method 2) | | | | | | | |
| 0.1 N HCl | 0.166 | 0.194 | 0.222 | 0.235 | 0.691 | 0.473 | 0.321 |
| Acetate buffer (pH 4.5) | 0.193 | 0.225 | 0.258 | 0.274 | 0.803 | 0.550 | 0.373 |
| Phosphate buffer (pH 6.8) | 0.171 | 0.199 | 0.228 | 0.242 | 0.709 | 0.486 | 0.330 |
| Dose numbers (Method 3) | | | | | | | |
| 0.1 N HCl | 0.427 | 0.427 | 0.427 | 0.427 | **1.154** | 0.672 | 0.380 |
| Acetate buffer (pH 4.5) | 0.496 | 0.496 | 0.496 | 0.496 | **1.341** | 0.781 | 0.441 |
| Phosphate buffer (pH 6.8) | 0.438 | 0.438 | 0.438 | 0.438 | **1.185** | 0.690 | 0.390 |

SmPC, summary of product characteristics. [a]The proposed volume is too conservative, especially for infants older than 6 months. Values in boldface correspond to Do > 1, which would lead to a solubility classification of 'not highly soluble'.

**Table 6** Dose numbers calculated from experimentally determined saturation solubility values of fluconazole in various buffered media, maintained at 37°C, using the maximum available dose strength (200 mg)

| Medium | Postconception (≤1 week) | Infants (0–6 months) | Infants (6–12 months) | Toddlers (1–3 years old) | Children (4–6 years old) | Children (7–12 years old) | Adolescents (13–18 years) |
|---|---|---|---|---|---|---|---|
| Dose numbers (Method 1)[a] | | | | | | | |
| 0.1N HCl | 0.996 | 0.996 | 0.996 | 0.996 | 0.996 | 0.996 | 0.996 |
| Acetate buffer (pH 4.5) | **1.158** | **1.158** | **1.158** | **1.158** | **1.158** | **1.158** | **1.158** |
| Phosphate buffer (pH 6.8) | **1.023** | **1.023** | **1.023** | **1.023** | **1.023** | **1.023** | **1.023** |
| Dose numbers (Method 2) | | | | | | | |
| 0.1N HCl | 0.771 | 0.566 | 0.406 | 0.318 | 0.230 | 0.158 | 0.107 |
| Acetate buffer (pH 4.5) | 0.896 | 0.658 | 0.472 | 0.369 | 0.268 | 0.183 | 0.124 |
| Phosphate buffer (pH 6.8) | 0.791 | 0.582 | 0.417 | 0.326 | 0.236 | 0.162 | 0.110 |
| Dose numbers (Method 3) | | | | | | | |
| 0.1N HCl | **1.98** | **1.25** | 0.78 | 0.58 | 0.39 | 0.22 | 0.13 |
| Acetate buffer (pH 4.5) | **2.30** | **1.45** | 0.91 | 0.67 | 0.45 | 0.26 | 0.15 |
| Phosphate buffer (pH 6.8) | **2.03** | **1.28** | 0.80 | 0.59 | 0.40 | 0.23 | 0.13 |

[a]The proposed volume is too conservative, especially for infants older than 6 months. Values in boldface correspond to Do > 1, which would lead to a solubility classification of 'not highly soluble'.

highly permeable definition and can be classified as BCS Class 1 in paediatric population akin to its classification in adults. Moreover, the 'safe space' for the dissolution time would be longer in the age groups where dose number is slightly higher because in these age groups gastric emptying is slower.

## Dissolution

The dissolution medium recommended by US-FDA and United States Pharmacopoeia (USP) for fluconazole 50 mg and 100 mg tablets and 50 mg/5 ml fluconazole for oral suspension is 500-ml water, apparatus II stirred at 50 rpm. For tablet strengths higher than 100 mg, and 200 mg/5 ml fluconazole for oral suspension, 900-ml water is recommended. WHO recommends 500 ml and 1000 ml of 0.1 N HCl for fluconazole 50 and 200 mg capsules, respectively, using paddle apparatus stirred at 100 rpm.

More than 85% fluconazole was released at 15 min from Diflucan capsules in 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer in basket apparatus stirred at 100 rpm (results not shown here).[20] Thus, fluconazole exhibits 'very rapid' dissolution characteristics according to the adult biowaiver procedure.[20]

Abdel-Rahman *et al.* quoted Professor Gordon Amidon, who suggested a minimum of 50% of drug release in 15 min to support a biowaiver decision for paediatric formulations; however, no dissolution volume was mentioned in that report.[22] Assuming dissolution and gastric emptying of liquids and small disintegrated solids (less than 2 mm) are first-order processes,[96–98] it is possible to estimate the respective rate constants, dissolution rate ($k_d$) and gastric-emptying rate ($k_{ge}$) as 2.8/h and 2.0/h, respectively.[99] Given that the absorption rate constant ($k_a$) of fluconazole is around 3.0/h,[100] it seems that a rapidly dissolving criterion will ensure that absorption of fluconazole is limited by gastric emptying ($k_a > k_d > k_{ge}$). Also, it is possible to identify a 'safe space' during development of new formulations containing fluconazole, because as long as $k_d$ in small intestinal media is substantially faster than $k_{ge}$, formulation influences on the pharmacokinetic profile should be negligible.[101] Because gastric emptying is slower in children (≤3 months),[102,103] the 'safe space' dissolution time for this group would be longer and so a complete dissolution within 30 min would also ensure that dissolution does not limit fluconazole absorption in this age group.

## Conclusions

The safety profile of fluconazole in children is excellent and is similar to its safety in adults. No unexpected safety concern specific to children has been reported. The physiological risk factors to absorption, including pH, gastric emptying, intestinal transit, membrane permeability and

metabolising enzymes do not appear to pose any risk to fluconazole absorption. We conclude that the BCS-based biowaiver recommended for adult fluconazole products can be extended to the paediatric population with similar requirements in excipient selection and dissolution profile comparison using BCS-based dissolution conditions.

## Declarations

### Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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