TDM monograph Isavuconazole

Summary

Indication:	Treatment of adults with: invasive aspergillosis, mucormycosis in patients for whom amphotericin B is inappropriate. (Candida infections are exempt from this guideline and require per patient evaluation.) Off-label indications: treatment of children with invasive aspergillosis and mucormycosis. Indication TDM: TDM may be considered (evidence level 4, for detailed information see monograph)
Sample material:	Serum or plasma
Time of sampling:	Trough concentration (C_{min}, just before next dose) 3 – 7 days after treatment initiation.
Storage conditions:	7 days at room temperature
Interpretation:	Reference values for the AUC_{24h} are 60 – 233 mg*h/L. Steady state trough levels of 2 – 4 mg/L correspond to an AUC_{24h} > 60 mg*h/L.
Evidence level:	4 (see TDM-monografie.org)

Contents

Introduction

Isavuconazole is a broad-spectrum triazole antifungal agent and shows activity against yeasts (*Candida* spp., *Cryptococcus* spp.), moulds (*Aspergillus* spp., and several fungi of the Mucorales order) and dimorphic fungi (Coccidioidomycosis, Histoplasmosis, Blastomycosis). It is approved for the treatment of invasive aspergillosis, and mucormycosis in adult patients for whom amphotericin B is inappropriate. Isavuconazole is administered orally or intravenously as the prodrug isavuconazonium sulphate.[1–4]

Dosing guidelines

Invasive aspergillosis / Mucormycosis

Adults: Intravenously as infusion (in ≥ 1 hour[3]) or per os: Day 1 + 2: 200 mg three times daily (loading regimen, 6 doses in total). Day 3 and further: 200 mg once daily.[3–5]
Isavuconazole (200 mg) is administered as isavuconazonium sulphate (372 mg), the prodrug of isavuconazole. Switching between the IV and oral formulations is acceptable; the same dose and frequency can be used and additional loading doses are not necessary.

Dosing guidelines in children and adolescents

Isavuconazole is not approved in children aged below 18 years of age.[3] The pharmacokinetics and safety of isavuconazole in children have been studied in a phase 1 study in 46 paediatric patients.[6]

Children *(off-label)*: Intravenously as infusion (in ≥ 1 hour[3]) or per os: Day 1 + 2: 5.4 mg/kg (max. 200 mg) three times daily (loading regimen, 6 doses in total). Day 3 and further: 5.4 mg/kg (max. 200 mg) once daily.[6,7]
Isavuconazole (200 mg) is administered as isavuconazonium sulphate (372 mg), the prodrug of isavuconazole. Switching between the IV and oral formulations is acceptable; the same dose and frequency can be used and additional loading doses are not necessary.

Dosing guidelines in patients with altered pharmacokinetics

No dose adjustments are required in case of renal impairment, dialysis or mild to moderate liver impairment.[3–5,8,9] The use of isavuconazole has not been investigated in patients with severe liver impairment (Child-Pugh class C) and is not recommended for these patients unless potential benefits outweigh the risks.[3] For critically ill patients or patients with (morbid) obesity, no *a priori* dose adjustments are recommended but therapeutic drug monitoring (TDM) may be indicated, see the relevant subsections of this monograph.[10,11]

Indications/Criteria for TDM

Currently, the additional value of TDM for isavuconazole is unclear. There is insufficient clinical evidence for a correlation between the isavuconazole concentration and either efficacy or toxicity of isavuconazole.[12–15] The pharmacokinetics of isavuconazole are linear and appear to be predictable.[13,16,17] The isavuconazole exposure seems sufficient with the standard dose of isavuconazole for the treatment of invasive aspergillosis and mucormycosis.[13,15,18] In the SECURE trial, an isavuconazole concentration between 1 – 7 mg/L was observed for >97% of the patients (n=160) treated with isavuconazole for invasive aspergillosis or infections by other filamentous fungi.[13] There was no clear correlation between plasma concentrations and efficacy outcomes.[13,15] Similarly, in the VITAL trial, in which patients (n=37) were treated with isavuconazole for mucormycosis, a relationship between plasma concentrations and efficacy outcomes could not be identified.[18] The intra-individual variability is approximately 20-30% between multiple isavuconazole measurements, suggesting that isavuconazole concentrations are consistent and predictable for the majority of patients.[13,14,19–21]
Considering the measured isavuconazole concentrations are consistent and show minimal variability, the absence of a clear exposure-outcome association, and the efficacy and safety of isavuconazole that is shown with the standard isavuconazole dose, routine TDM for isavuconazole is not recommended.[5,12–15,17,20,22,23] TDM may be considered in specific circumstances or subpopulations.

TDM of isavuconazole may be considered in the following cases: [5,10,22,24–29]

- Treatment of sanctuary sites of infection, such as the central nervous system (CNS);
- Infections caused by less susceptible micro-organisms (e.g. MIC >1 mg/L);
- Suspected lack of efficacy;
- Suspected non-compliance;
- Hepatotoxicity or other unexplained toxicity;
- Severe liver dysfunction;
- Drug interactions that may affect isavuconazole concentrations;
- Suspected reduced oral absorption;
- (Morbid) obesity;
- Patients < 18 years;
- Critically ill patients/Patients receiving extracorporeal membrane oxygenation (ECMO).

Reference values

An optimal therapeutic range has not yet been established for isavuconazole and there is no clear relationship between exposure and clinical outcome.[12,13,15] However, in case of TDM, the following reference values should be considered: steady state trough levels of 2 – 4 mg/L, C_{min} up to 8 mg/L may be acceptable.[6,11,13–15,28,30–32]

The relevant PK/PD parameter for isavuconazole is AUC/MIC ratio.[3,13,31] Therefore, ideally an AUC of isavuconazole should be measured when TDM is performed. Reference values for the AUC_{24h} are 60 – 233 mg*h/L.[6,15] Steady state trough levels can serve as a proxy to determine the exposure of isavuconazole in clinical practice. Steady state trough levels of 2 – 4 mg/L correspond to an AUC_{24h} > 60 mg*h/L and are considered appropriate for *Aspergillus* infections, but trough levels up to 8 mg/L may be acceptable.[6,11,13–15,28,30–32] Note that *Mucor* infections may require concentrations > 4 mg/L due to higher MICs (expert opinion).[33]

Several pharmacokinetic studies estimated the mean exposure of isavuconazole. They showed that the standard dosing regimen in the majority of patients lead to estimated isavuconazole exposure that was sufficient to achieve the established target (AUC/MIC ratio), which was based on preclinical data.[11,31,34]

The relationship between the measured isavuconazole trough concentration and the efficacy and safety of isavuconazole was investigated in 231 adult patients. The median isavuconazole trough concentration in steady state was 3.2 mg/L (range: 1.7 – 11.0 mg/L) with a median exposure (AUC_{24h} at steady state) of 90 mg*h/L (range: 10 – 343 mg*h/L). No statistical difference was found between isavuconazole exposure and the efficacy of the treatment (based on all-cause mortality through day 42, overall response and clinical response at end of treatment).[15]

Efficacy

For the primary treatment of suspected invasive mould disease isavuconazole was found to be non-inferior and well tolerated compared to voriconazole. All-cause mortality was 19% for isavuconazole (n=48) and 20% for voriconazole (n=52) in the intention-to-treat population.[16]
For the treatment of mucormycosis isavuconazole was found to show activity against mycormycosis with response rates similar to those reported for amphotericin B. In this single arm, open label study, isavuconazole was well tolerated, with an all-cause mortality of 33% for isavuconazole (n=21) and 39% for amphotericin B (n=33).[18]

Relationship with occurrence of side effects

There is insufficient clinical evidence for a correlation between the isavuconazole concentration and the occurrence of side effects or toxicity.[12,15]

Toxicity

Isavuconazole appears to be less toxic and better tolerated than voriconazole.[5,8,12,16] Isavuconazole showed less liver toxicity (9% versus 16%), neurological side effects (15% versus 27%) and skin disorders (33% versus 42%) compared to voriconazole and the number of drug-related adverse events was 42% for isavuconazole and 60% for voriconazole.[16] Gastro-intestinal complications appear to be a common side effect of isavuconazole.[16,19] There seems to be no clear correlation between the isavuconazole trough concentration and the occurrence of liver toxicity. Therefore, no clear upper limit for toxicity for the isavuconazole concentration is established.
In contrast to other triazoles, isavuconazole was not associated with QTc interval prolongation. Isavuconazole shortens the QTc interval in a concentration-related manner.[3,12,35] In a study with 26 patients, QTc interval shortening was observed for 24 patients after treatment initiation with isavuconazole. The mean decrease was 7.4% (36.6 ± 38.8 ms, range 7-202 ms).[36]

Sampling conditions

If TDM is performed, an isavuconazole trough concentration can be collected 3 – 7 days after treatment initiation, provided that a loading dose regimen has been given.[10,32] Following isavuconazole administration according to licensed dosing, steady state concentrations are expected between day 3 and 7 of therapy. TDM may therefore be performed from day 3 onwards. The isavuconazole trough concentration may further increase during long-term treatment due to its long half-life (110-130 hours) or in certain patient subpopulations.[19,31,37]

There are no guidelines available to guide dosing of isavuconazole if TDM of isavuconazole is performed.[37] If a high trough concentration is measured and patients experience adverse events that could be caused by isavuconazole, a lower isavuconazole dose can be considered.[38] Depending on the severity of the adverse event, the dose can be adjusted from 200 mg per day to alternately 200 mg and 100 per day or 100 mg per day.[38] If a low trough concentration is measured, the maintenance dose may be increased and an extra loading dose of isavuconazole may be considered to achieve an adequate steady-state concentration more

rapidly. It should be taken into account that due to the long half-life of isavuconazole, steady state is reached after approximately 3 – 4 weeks after dose adjustment.[37] In case TDM of isavuconazole is considered, it is advised to monitor isavuconazole trough concentrations once weekly, but individual cases may require less frequent monitoring.[32]

Additional information concerning the interpretation of results

Background information [extended]

Registration trials

The SECURE trial was a phase 3, double-blind, global multicentre, comparative-group study, investigating the efficacy and safety of isavuconazole versus voriconazole in patients with an invasive fungal infection. In total, 516 adult patients were included with an invasive fungal infection. Half of these patients (n = 258) received isavuconazole, while the other half (n = 258) received voriconazole. An isavuconazole concentration between 1 – 7 mg/L was observed for >97% of the patients (n=160) treated with isavuconazole.[13] This study showed non-inferiority of isavuconazole compared to voriconazole for the primary treatment of invasive mould disease. Compared with voriconazole, fewer drug related adverse events were observed with isavuconazole (60% vs. 42% respectively).[16]

The efficacy of isavuconazole for mucormycosis was investigated in a single-arm, open label trial (VITAL study). In this study, 37 patients were included aged 18 years or older with proven or probable mucormycosis. Patients received isavuconazole as primary treatment or because amphotericin B was inappropriate. Based on the results of this study, isavuconazole showed activity against mucormycosis and was well tolerated.[18]

Pharmacodynamics

Isavuconazole is the active substance formed after oral or intravenous administration of isavuconazonium sulphate. Isavuconazole inhibits lanosterol 14-alpha-demethylase, which is responsible for the conversion of lanosterol to ergosterol, a key component of the fungal cell membrane. This weakens the structure and function of the fungal cell membrane.[3,33]

Pharmacokinetics

Isavuconazole is administered as a prodrug (i.e. isavuconazonium sulphate), which can be administered intravenously or orally. After administration, isavuconazonium sulphate is rapidly hydrolysed by plasma esterases to the active moiety isavuconazole.[3] The pharmacokinetics of isavuconazole are linear and after repeated administration both the de AUC_{∞} and C_{max} increase proportionality with the dose.[30,39,40] CRP does not seem to be associated with C_{min}, contrary to voriconazole.[30]

PK parameters

	F (%)	**Cl** (L/h^{-1})	**V_d** (L)	**$t_{1/2}$** (h^{-1})	Protein Binding (%)	T_{max} (h)	Ref.
Adults	> 98	2.3-2.5*	200-500	110	>99[#]	2-3	3,5,11

* For Asian populations a clearance of 1.5 L/h is observed.

[#] Protein binding may vary in subpopulations, such as ICU patients.[41]

Population models

Population	Model	**Vd** (L) / **F**	**CL** (L/ h^{-1}) / **F**	Ref.
Adults (healthy subjects, patients, non ICU)	Two-compartment model, IV/p.o. administration	V_1: 49.3 (95%CI: 46.1 – 52.2) V_2: 418.1 (95%CI: 381.5 – 453.0)	2.36 (95%CI: 2.25 – 2.46)	11
ICU patients with CAPA*	One-compartment model, IV administration	837 (95%CI: 572 – 1102)	3.97 (95%CI: 3.11 – 5.02)	22
Transplant recipients¥	Two-compartment model, IV administration	V_1: 57.0 (95%CI: 43.9 – 71.4) V_2: 465.5 (95%CI: 401.3 – 547.7)	4.22 (95%CI: 3.32 – 5.19)	34
Adults (non ICU)	One-compartment model, IV/p.o. administration	361.2 (SD: +/- 166.3)	2.5 (SD: +/- 1.6)	31

* CAPA: Covid-19-associated pulmonary aspergillosis.
¥ Solid-organ transplant recipients receiving peritransplant prophylaxis.

Absorption

The bioavailability of isavuconazole after oral administration is approximately 98% in adults. The absorption of isavuconazole seems to be not affected by food or acidic gastric conditions.[42] After oral administration the maximum plasma concentration is reached after approximately 2-3 hours, for intravenous administration the maximum plasma concentration is reached at the end of infusion (the infusion time must be at least 1 hour).[3] The maximum plasma concentration for both routes of administration is similar in healthy volunteers.[33,43]
Based on the results of two studies in adult transplant patients, isavuconazole can also be administered via enteral feeding tube by opening the capsules. Subsequently, the content of the capsules should be diluted in water and administered via the enteral feeding tube. A comparable isavuconazole concentration was found between administration via enteral feeding tube and oral or intravenous administration.[44,45] In paediatric patients this method resulted in reduced isavuconazole exposure, as shown in a study in 17 paediatric patients.[46] Administration of the intravenous solution via enteral feeding tube has shown comparable exposure to oral administration of isavuconazole capsules in adults and may therefore be a suitable alternative.[47]
Patients with haematological malignancies can develop mucositis due to intensive chemotherapy. In a study with 56 patients with mucositis at therapy onset who received oral isavuconazole, no significant difference was found in isavuconazole exposure compared with patients without mucositis. However, an important limitation of this study was that the severity of mucositis was not known. Although oral isavuconazole in patients with severe mucositis may be possible, intravenous administration may be preferred.[48]

Distribution

In healthy volunteers, isavuconazole is highly bound to proteins (> 99%), predominantly to albumin.[3] Protein binding may be decreased in subpopulations, such as ICU patients, resulting in a higher unbound fraction of isavuconazole.[41] Binding to or accumulation in erythrocytes is minimal.[40] Isavuconazole has a steady state volume of distribution of approximately 450 L and is thought to be extensively distributed in various tissues. However, the exact distribution to specific types of tissues is not known.[3,11,42] Therapeutic isavuconazole concentrations are expected to be achieved in the brain based on animal studies and several case-reports. Isavuconazole may poorly penetrate within an abscess.[49,50]

Metabolism

Isavuconazoniumsulphate is a prodrug that is rapidly hydrolysed to isavuconazole. Isavuconazole is metabolized in the liver by cytochrome P450 enzymes (CYP3A4 and CYP3A5) and UGT. The metabolites of isavuconazole have no antifungal activity.[1,42] None of the individual metabolites of isavuconazole have an AUC > 10% for the total drug-related exposure.[3,40]

Elimination

The metabolites of isavuconazole are excreted for 45.5% in urine and 46.1% in faeces. Approximately 33% of the total drug dose was recovered as unchanged isavuconazole in the faeces and < 1% of the dose was recovered in urine.[40] The half-life of isavuconazole in patients is estimated to be 110 hours.[3,11]
The clearance of the population was approximately 2.4 L/h. However, in Asian populations clearance seems approximately 36% lower compared with Caucasians and is estimated to be 1.5 L/h. It is not clear why the clearance may be lower in Asians.[11]
A loading dose regimen is advised for the first 48 hours due to the long half-life of isavuconazole. Without an adequate loading dose, steady-state is assumed to be reached after approximately 3 – 4 weeks.[39] By administering an adequate loading dose regimen, an isavuconazole concentration between 2 – 4 mg/L is rapidly reached.[19]

Paediatric population

Isavuconazole is not approved in children aged below 18 years of age.[3] The pharmacokinetics and safety of isavuconazole in children has been studied in a phase 1 study in 46 immunocompromised paediatric patients.[6] Of these patients, 27 received isavuconazole intravenously (1 to < 6 years n = 9; 6 to < 12 years n = 8; 12 to < 18 years n = 10) and 19 received isavuconazole orally (6 to < 12 years n = 9; 12 to < 18 years n = 10). For intravenous administration, patients received a loading dose of 5.4 mg/kg isavuconazole (as (10 mg/kg) isavuconazonium sulphate, cut-off for body weight ≤ 37 kg) every 8 hours for 6 doses, followed by a maintenance dose of 5.4 mg/kg (with a maximum of 200 mg) once daily. Patients > 37 kg received a loading dose of 200 mg every 8 hours for 6 doses, followed by a maintenance dose of 200 mg once daily. For oral administration of isavuconazole, a cutoff for body weight of 32 kg was used instead of 37 kg (for greater dosing accuracy due to fixed capsule strength) with the same dosing regimen as for intravenous dosing of isavuconazole. In this study, isavuconazole, administered intravenously or orally, was generally well-tolerated in children, displaying a safety profile comparable to that observed in adults. Intravenous administration resulted in a similar isavuconazole exposure to that of adults for approximately 80 – 87% of the paediatric participants and oral administration yielded a range of about 76 – 87%.[6]
In addition, a retrospective observational study in 15 paediatric patients with a combined total of 111 trough levels reported on the TDM of isavuconazole in real-world practice.[7] Patients in this study received a loading dose of 5.4 mg/kg isavuconazole (as (10 mg/kg) isavuconazonium sulphate, cut-off for body weight ≤ 35 kg) every 8 hours for 6 doses, followed by a maintenance dose of 5.4 mg/kg (with a maximum of 200 mg) once daily. Patients > 35 kg received a loading dose of 200 mg every 8 hours for 6 doses, followed by a maintenance dose of 200 mg once daily. The same dosing regimen was used when patients switched to oral administration. The study showed that this dosing regimen was generally well-tolerated and may be adequate to achieve therapeutic levels in paediatric patients. Patients receiving ECMO may require higher dosages.[7]

Elderly

No dose adjustment is necessary for elderly patients; however, the clinical experience in elderly patients is limited.[3]

Obesity

In literature, there is limited information available regarding isavuconazole exposure in patients with (morbid) obesity. Based on pharmacokinetic population models and a study in critically ill ICU patients, a potential correlation between patient weight or BMI and the volume of distribution of isavuconazole has been suggested.[11,21,22,31,34] In this context, the volume of distribution might increase as patient total body weight increases. Therefore, due to the lack of data on treatment with isavuconazole in patients with (morbid) obesity, TDM of isavuconazole could be considered.

Pregnancy and breast-feeding

There are no data on the use of isavuconazole in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Isavuconazole must not be used during pregnancy except in patients with severe or potentially life-threatening fungal infections, in whom isavuconazole may be used if the anticipated benefits outweigh the possible risks to the foetus. Available pharmacodynamic/toxicological data in animals have shown excretion of isavuconazole and its metabolites in milk. Breast-feeding should therefore be discontinued during treatment with isavuconazole.[3]

Renal impairment

Renal impairment (in general):	No dose adjustment of isavuconazole is necessary in patients with renal impairment, including patients with end-stage renal disease.[3,5,51]
Renal replacement therapy:	Isavuconazole is not removed by hemodialysis.[3] Evidence suggests that isavuconazole is removed by low-efficiency dialysis[52], but this does not seem to apply to continuous renal replacement therapy.[53] However, the literature on this matter is inconclusive.[25] At present, adjusting the dosage of isavuconazole during renal replacement therapy is not recommended.[9]

Liver impairment

Compared to voriconazole, isavuconazole exhibits lower hepatotoxicity.[16] The clearance of isavuconazole appears to be reduced in cases of mild (Child-Pugh class A) and moderate (Child-Pugh class B) liver impairment (1.6 L/h and 1.3 L/h, respectively). Hence, the average trough concentration of isavuconazole is higher in individuals with mild and moderate liver impairment compared to healthy volunteers. Based on pharmacokinetic data, along with a similar adverse event profile observed in healthy volunteers and individuals with mild to moderate liver impairments, dosage adjustment of isavuconazole does not seem necessary for patients with such impairments.[54] The use of isavuconazole has not been investigated in patients with severe liver impairments (Child-Pugh class C) and is not recommended for these patients unless potential benefits outweigh the risks.[3] In cases of severe liver impairment combined with adverse effects that might be attributed to isavuconazole, TDM of isavuconazole could be considered.

Critically ill patients

Isavuconazole plasma concentrations and isavuconazole protein binding may vary in critically ill patients.[10,21,22] A study with 41 ICU patients showed C_{min} levels < 1 mg/L in 32% of the measurements (n = 83). In addition, isavuconazole peak and trough levels were significantly lower in patients with a BMI ≥ 25 and with higher SOFA scores.[21] Subtherapeutic isavuconazole exposure may be seen in ECMO patients and an increased loading dose may be required.[55] Similar results were observed in a retrospective study in paediatric patient receiving ECMO (n=3).[7] However, it remains unclear if this may be due to the ECMO or because of critical illness itself. TDM in critically ill patients with or without ECMO could therefore be considered.[24–27,56]

Pharmacogenetics

It is unknown if pharmacogenetics lead to alterations in clearance of isavuconazole. There is no literature available suggesting dose recommendations. In individuals with CYP3A5 activity (i.e., CYP3A5 expressors), theoretically an increased metabolism of isavuconazole might be observed, potentially leading to lower isavuconazole exposure. However, there is currently no evidence suggesting that CYP3A5 activity results in inadequate isavuconazole exposure.[57]

Interactions

Isavuconazole seems to have fewer interactions than other triazoles.[58–60] Isavuconazole is a substrate and a moderate inhibitor of CYP3A4 and CYP3A5. Weak to moderate CYP3A4/5 inducers can reduce isavuconazole concentrations, and TDM might be considered in situations where simultaneous use of these drugs cannot be avoided.[3,61] Simultaneous use of strong CYP3A4/5 inducers such as rifampicin, is contraindicated, as they can decrease the AUC of isavuconazole by 90%.[3,62] Literature suggests that the exposure to isavuconazole might be reduced when given simultaneously with flucloxacillin. Therefore, TDM of isavuconazole is advised if the patient is simultaneously treated with isavuconazole and flucloxacillin.[63,64]
No dosing adjustments are advised when isavuconazole is co-administered with moderate or strong CYP3A4 and CYP3A5 inhibitors. However, side effects or toxicity of isavuconazole may increase and TDM could therefore be considered.[3,61,62] The metabolism of various immunosuppressants (e.g. tacrolimus, sirolimus, and cyclosporine) can be inhibited by isavuconazole. The degree of inhibition is unpredictable and therefore close monitoring of the immunosuppressant is recommended.[12,42,65–67] Furthermore, isavuconazole is a mild inducer of CYP2B6, a slight inhibitor of P-gp, OCT2, and UGT and *in vitro,* isavuconazole is a BCRP inhibitor.[3,42,68]

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Colophon

This guideline has been constituted by Dr. A. Veringa, hospital pharmacist – clinical pharmacologist, Dr. J. Rozema, hospital pharmacist i.t., M.L. Toren-Wielema, MSc., hospital pharmacist – clinical pharmacologist, Dr. T.H. Oude Munnink, hospital pharmacist – clinical pharmacologist, A.M.E. Jansen, MSc., hospital pharmacist i.t., Dr. R.J.M. Brüggemann, hospital pharmacist-clinical pharmacologist, Dr. M.G.G. Sturkenboom, hospital pharmacist – clinical pharmacologist/toxicologist ERT, under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)
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Appendices

Not applicable

Revision

Not applicable