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A REVIEW ON ISAVUCONAZOLE AS AN ANTIFUNGAL DRUG

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ABSTRACT

Isavuconazole is a triazole antifungal drug. It is used in treatment of invasive aspergillosis and invasive mucormycosis in adult. Many researchers and scientists are working on Isavuconazole drug.The main purpose of of this review paper is to gives the detailed Isavuconazole and current research on Isavuconazole. It is available in various dosage forms. Isavuconazole is administered by oral and intravenous route. In this review we concentrated on history, pharmacokinetics, and mechanism of action of Isavuconazole. In this review also includes the interactions of drug with their adverse reactions and uses of Isavuconazole drug.This review also gives the idea about various analytical techniques are used for quantative determination of Isavuconazole in various pharmaceutical dosage form.

KEYWORDS: Isavuconazole, Pharmacokinetics, Drug-drug interactions.

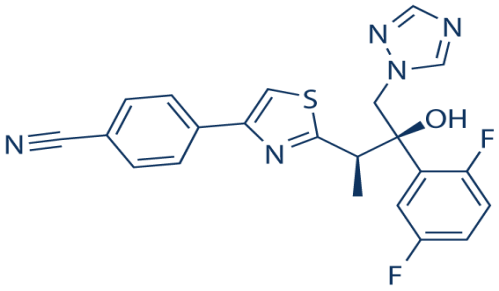
INTRODUCTION

Antifungal drugs are used in treatment of fungal infections. There are two types of antifungal drugs i.e. local and systemically. Isavuconazole is used systemically.[1] Isavuconazole is water soluble prodrug with broad spectrum antifungal activity opposed to yeast and molds.

Isavuconazole was found in Japan. The researchers at Roche's research center in Kamakura.[2,3]

In 2010 Basilea complete phase lll trials, gets regulatory approvals and market the drug.In 2013 and 2014 Astellas Pharma who was partner of Basilea won orphan drug designation in U.S. for isavuconazonium for treating invasive aspergillosis, invasive mucormycosis and invasive candidiasis.[4,5,6,7]

In March 2015 US Food Drug Administration granted approval,[8] and In October 2015 European Medicines Agency approved Isavuconazole. In 2017 Basilea licensed rights to Pfizer to market Isavuconazole in Europe and other countries.[9,10,11] See the below structure of Isavuconazole with IUPAC name.



IUPAC NAME: 4-{2-[(2R, 3R)-3-(2,5-difluorophenyl)-3-hydroxy-4-(1H-1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl}benzonitrile

Table 1: Physical properties of Isavuconazole.

Sr. no	Properties	Values
1	State	Solid
2	Appearance	White powder
3	Molecular Formula	C22H17F2N5OS
4	Molecular Weight	437.5
5	Biological half life	130 hr
6	Pka(strongest acidic)	12.59

7	Pka(strongest basic)	2.32
8	Refractivity	123.94m² mol -¹
9	Water solubility	0.0162mg/ml
10	Storage Condition	2-8^{0}c
11	Assay	98% HPLC

On oral administration of 200mg Isavuconazole drug the mean plasma concentration at steady state was 7499ng/ml. If administration of 600mg Isavuconazole drug Cmax at steady state was 20028ng/ml and if administration of 400mg resulted in mean AUC of 189462ng/ml. Isavuconazole can be taken with or without Food but if taken high fat meal decreased oral Isavuconazole Cmax by 9%.[12] Isavuconazole is excreted 46%in faeces and 45.5% in urine. It is available in oral and intravenous formulations.The Pharmacokinetic parameters of Isavuconazole are given below:

Table 2: Pharmacokinetic parameters of Isavuconazole.

Sr.no	Parameters	Values
1	Bioavailability	98%
2	Half life	100-130hours
3	Volume of distribution	400-500lit
4	Protein binding excretion	790%
5	Renal excretion	Mora than 1%

Isavuconazole displays fungicidal actions by disrupting the biosynthesis of ergosterol, which is a key component of fungal cell membrane. It inhibits cytochrome P-450 dependent enzyme lanosterol 14-alpha-demethylase that mediates the conversion of lanosterol to ergosterol. The side arm of of the active isavuconazole molecule allows for greater affinity for the binding pocket in the fungal CYP51 protein by orienting the triazole ring of the molecule to engage with the heme moiety at the bottom of the binding pocket. This explains the wide antifungal spectrum of isavuconazole and possible cross-resistance to other triazoles. As a result of lanosterol 14-alpha-demethylase inhibition, toxic methylated sterol precursors such as 14-α-methylated lanosterol, 4, 14-dimethylzymosterol, and 24-methylenedihydrolanosterol alter the function of fungal membrane and accumulate within the fungal cytoplasm. Depletion of ergosterol within the fungal cell membrane leads to decreased structural integrity and function of the cell membrane, inhibited fungal cell growth and replication, and ultimately cell death.[13,14,15,16]

Dose and Administration

CRESEMBA **is** brand name of isavuconazonium sulfate. Each capsules of CRESEMBA holds 100mg isavuconazole means 186.3mg³isavuconazonium sulfate. Loading dose is an first greater dose of drug that given at the preliminary of course treatment before dropping down to a lower maintenance dose,[17] and Maintenance dose means maintenance rate of drug administration is equal to rate of excretion at steady state.[18]

Table 3: Dose and administration of Isavuconazole (100mg Capsule).

Dose	Loading dose	Maintenance
CRESEMBA 100mg Capsule	2 capsules (200mg of Isavuconazole) Given by oral route to every 8 hours for first 48 hours (6doses)	2 capsules (200mg of Isavuconazole) Given by oral route to once daily starting 12 to24 hours after last loading dose.

CRESEMBA for Injection

Each vial of CRESEMBA contains 200mg of Isavuconazole 372mg² of isavuconazonium sulfate.

Table 4: Dose and administration of Isavuconazole (200mg Capsule).

Dose	Loading dose	Maintenance
CRESEMBA 200mg Capsle	1 Reconstituted vial (200mg of Isavuconazole) Intravenously every 8 hours for first 48 hours (6doses)	1 Reconstituted vial (200mg of Isavuconazole) Intravenously once daily.

Table 5: Adverse effects of Isavuconazole.

Adverse reactions	Adverse reactions observed to discontinuation of Isavuconazole during clinical trials
Nausea	Confusion state
Vomiting	Acute renal failure
Diarrhea	Increase blood bilirubin
Headache	Confusion
Hypokalemia	Dyspnoea
Constipation	Epilepsy
Dyspnea	Respiratory failure
Cough	Vomiting

Drug Interactions

Coadministration of isavuconazonium sulfate with strong CYP3A4 inhibitors is contraindicated because this products increase plasma concentration of Isavuconazole markedly.

Interactions between Isavuconazole and other coadministred product/medicine are as follows.

Table 6: Drug Interactions of Isavuconazole.

Sr. No.	Category of drug	Coadministration of medicinal products	Effect of drugs	Advise
1	Anticonvulsant	Carbamazepine + Isavuconazonium sulfate (Strong CYP3A4/ 5 inducer)	Anticonvulsant decreases the level of isavuconazonium sulfate by affecting CYP3A4 enzyme metabolism.	Contraindicated
2	Antibacterial	Rifampicin + Isavuconazole (Strong CYP3A4/ 5 inducer	Metabolism Decreased	Contraindicated
3	Antifungal	Ketoconazole +Isavuconazonium sulfate (Strong CYP3A4/ 5 inducer	Increase effect of isavuconazonium sulfate by affecting CYP3A4 enzyme metabolism.	Contraindicated
4	Immunosupressants	Prednisolone + Isavuconazonium sulfate	Prednisolone increases level of isavuconazonium sulfate by affecting on CYP3A4/ 5 metabolism	Use with caution
5	Anticancer	Natural alkaloids: Vincristine, Vinblastin (P-gp substrate)	Increase effect of Isavuconazonium sulfate	Use with caution
6	Antidiabetics	Metformin +Isavuconazole (OCT1,OCT2,MATE Substrate)	Increases concentration of serum	Use with caution
7	Anti-coagulants	Warfarin + Isavuconazole (CYP2C9 substrate)	Increases the concentration of serum	Use with caution
8	Antiviral	Lopinavir + Isavuconazonium sulfate CYP3A4/ 5 strong inhibitors and substrate	Increases level of isavuconazonium sulfate	Contraindicated
9	Antacids	Omeprazole + Isavuconazonium sulfate (CYP2Cl9 substrate and increases gastric pH)	Decrease metabolism of isavuconazole	Use with caution
10)	Antigout	Colchicine + Isavuconazonium sulfate (P-gp substrate)	Decreases level of isavuconazonium	Required dose adjustment

There are various analytical techniques are used for quantative determination of Isavuconazole in pharmaceutical dosage form .The methods includes High-Performance Liquid Chromatography (HPLC),High-Performance Thin Layer Chromatography (HPTLC),Fluorescence based high performance liquid chromatography, UV,and Assay methods includes liquid chromatography- Tandem mass spectroscopy (LC-

MS/MS), LC with UV detection (LC-UV),LC with Fluorescence (LC-FL) and bioassay.This methods are important to determine or check quality, accuracy of medicine which are available in market.

Table 7: Various method used for determination of quality, accuracy of Isavuconazole.

Sr. No.	Sample	Method	Application
1	Plasma	HPLC-UV	Used for quantitative study of drug.
2	Plasma	HPLC	Used for Therapeutic Dose Monitoring of Isavuconazole.
3	Serum	UPLC-MS/MS	Used for pharmacokinetics study of isavuconazole, itrakonazole,fluconazole
4	Plasma	Assay method LC-MS/MS,LC-UV,LC-FL	Used to check accuracy and reproducibility. Compared with known concentration of sample.
5	Plasma	Fluorescence based HPLC	Used for analytical purposes

CONCLUSION

The present review article we have discussed the history of Isavuconazole. The researcher or scientist work on development of Isavuconazole was found in numerous literatures. In this article revealed the pharmacokinetics, pharmacodynamics, and various drug interactions of Isavuconazole drug was discussed. Various methods used for determination of Isavuconazole quality accuracy and safety that can be discussed in this paper this review on Isavuconzaole will be useful for development of drug delivery system which helps in the understanding the applications.

REFERENCES

1. Benitez, Lydia L., Carver, Peggy L., "Adverse effects associated with long term administration of azole antifungal agents", 2019; 79(8): 833-853.
2. Guinea J, Bouza E. "lsavuconazole a new and comprising antifungal triazole for the treatment of Isavuconazole of invasive fungal infections " Future Microbiology, December 2008; 3(6): 603.
3. Cresemba Capsules and Cresemba powder for injection,U.S., FDA, 6 March 2015.
4. Ohwada J.,Tsukazaki M., Hayase T.,Ottawa N.,Ishikawa,fukudaH,(January)"Design,synthesis and antifungal activity of a novel water soluble prodrug of anti triazole",Bio-organic and Medicinal Chemistry Letters, 2003; 13(2): 191-6.
5. "Isavuconazonium sulfate orphan drug designation and approvals" U.S. Food and Drug Administration (FDA), 6 May 2013.
6. "Isavuconazonium sulfate orphan drug designation and approvals" U.S. Food and Drug Administration (FDA), 20 October 2014.
7. "Isavuconazonium sulfate orphan drug designation and approvals" U.S. Food and Drug Administration (FDA), 25 October 2013.
8. Petit N.N.,Carver P.L., " Isavuconazole -A new option for the management of invasive fungal infections",The annals pharmacotherapy, July2015; 825-842.
9. Elvidge S (16 June), "Pfizer builds out anti-infective reach with Basilea deal", Biopharma dive, 2017.
10. "Pfizer enters into agreement to develop and commercialization rights in Europe for Cresemba, a novel treatment for potentially life threatening fungal infection among immunocompromised patients, 14 June 2017.
11. "Pfizer enters into agreement to develop and commercialization Cresemba in China and Asia pacific region, 30 November 2017.
12. EMA Label: Cresemba, Isavuconazole-European Medicines Agency-Europa EU.
13. Donnelley MA, Zhu ES, Thompson GR 3rd, Isavuconazole in the treatment of invasive aspergillosis and mucormycosis infections, Infect Drug Resistance, 2 Jun 2016; 79-86.
14. Kovanda LL, Desai AV, Lu Q.,Townsend RW., Akhtar S., Bonate P., Hope W.W., Isavuconazole Population Pharmacokinetic Analysis Using Nonparametric Estimation in Patients with Invasive Fungal Disease, antimicrobial agents Chemother, 22 Jul 2016; 4568-4576.
15. Falci DR, Pasqualotto AC: Profile of isavuconazole and its potential in the treatment of severe invasive fungal infections, Infect Drug Resistance, 22 October 2013; 163-174.
16. Ellsworth, M. and Ostrosky-Zeichner, L. Isavuconazole: Mechanism of action, clinical efficacy, and resistance. Journal of Fungi, 2020; 6(4): 324.
17. Cp verses time-iv infusion with loading dose archived from the original on, 16 February 2016.
18. Houglum, Joel, Harrelson, Gary, Principles of pharmacology for athletic trainers, SLACK incorporated, 51.