NEW DRUGS

Isavuconazole

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Approved indication: invasive fungal infections

Cresemba (Pfizer)
100 mg capsules, vials containing 200 mg powder for injection

Isavuconazole, which comes in the form of a prodrug isavuconazonium sulfate, is a triazole antifungal indicated for adults with invasive aspergillosis. It is also approved for the rare condition of invasive mucormycosis when amphotericin B is not appropriate. Like other drugs in the class, it works by inhibiting the synthesis of ergosterol which is an essential part of the fungal cell membrane.

The approval of isavuconazole is based on two main clinical studies – the SECURE trial[1] and the VITAL trial.[2] The SECURE trial was a phase III non-inferiority study comparing isavuconazole with voriconazole. It enrolled patients with invasive fungal disease mainly caused by *Aspergillus* species (e.g. *A. fumigatus, A. flavus, A. niger* and *A. terreus*). Some patients had other fungi isolated including unidentified filamentous fungi. Over 80% of the patients had a haematological malignancy, 20% had had a stem cell transplant and 66% had neutropenia at baseline.

Patients randomised to isavuconazole (n=258) were started on the intravenous formulation (200 mg three times a day), then continued or switched to capsules (200 mg daily) on the third day. Patients assigned to voriconazole (n=258) were given the drug intravenously on days one and two (6 mg/kg twice daily then 4 mg/kg twice daily) and then continued (4 mg/kg intravenously twice daily) or switched to oral voriconazole (200 mg twice daily) on day three. After a median of 45 and 47 days of treatment, all-cause mortality rates for isavuconazole and voriconazole were similar – 19% versus 20%. The corresponding treatment response rates in patients with proven or probable invasive aspergillosis were 35% and 36%.[1]

The VITAL trial was an open-label, single-arm study that enrolled 37 patients with proven or probable invasive mucormycosis. This included previously treated and treatment-naïve patients. Fungi identified at baseline included *Mucorales* moulds, *Mucor* species, *Rhizomucor* species, *Rhizopus oryzae* and *Lichteimia corymbifera*. Participants received the same isavuconazole dosing regimen as in the SECURE trial for a median of 84 days. By the end of the trial, 14% of the patients had a complete response to treatment. All-cause mortality was 43%.[2]

In a safety cohort of 403 patients, the most common adverse effects related to isavuconazole included nausea (7.4% of patients), vomiting (5.5%), dyspnoea (3.2%), abdominal pain (2.7%), diarrhoea (2.7%), injection-site reactions (2.2%), headache (2%) and rash (1.7%).

Skin, eye and hepatobiliary disorders were less common with isavuconazole than with voriconazole. In the SECURE trial, elevated liver laboratory tests were reported in 17.1% of patients in the isavuconazole group and 24.3% in the voriconazole group. Liver function should be tested before and during treatment. Isavuconazole is not recommended in those with severe liver impairment.

As isavuconazole shortens the QTc interval, it is contraindicated in patients who have familial short QT syndrome.

Isavuconazole is a pregnancy category D drug and is not recommended during pregnancy. In animal studies, it was associated with dose-related increases in fetal rib abnormalities. It is also not recommended during lactation as there was evidence of its excretion in the milk of lactating rats.

Isavuconazole has many potential drug interactions so it is prudent to consult the product information before prescribing in patients taking other medicines. Isavuconazole should not be given with concomitant ketoconazole, high-dose ritonavir (>200 mg/12 hourly) or drugs that strongly induce cytochrome P450 (CYP) 3A4/5 (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort). It is also contraindicated with moderate CYP3A4/5 inducers (e.g. efavirenz, nafcillin, etravirine). Concomitant use with mild inducers should also be avoided.

Isavuconazole may increase exposure to drugs that are metabolised by CYP3A4/5 such as tacrolimus, sirolimus and ciclosporin. Therapeutic monitoring and dose adjustment of these drugs may be needed. Dose adjustment may be needed for substrates of P-glycoprotein as toxicity may be a concern, particularly with drugs that have a narrow therapeutic index such as digoxin, colchicine and dabigatran.

This antifungal comes in the form of a water-soluble prodrug, isavuconazonium sulfate, which can be given intravenously or orally. Following administration, it is rapidly hydrolysed to isavuconazole by esterases in plasma. Maximum concentrations of this active metabolite are reached within 2–3 hours of oral administration. Food does not affect absorption. It is mainly metabolised by CYP3A4/5 and uridine diphosphate-glucuronosyltransferases. The product information recommends that no dose adjustment is required in renal or hepatic impairment. The drug has not been studied in severe hepatic impairment.

Isavuconazole appears to be non-inferior to voriconazole for patients with invasive aspergillosis.

It was also of benefit in some patients with invasive mucormycosis. However, the trial was small with no comparator and the activity of isavuconazole on individual fungi was difficult to assess.[2] It is not known how isavuconazole will compare to other azole antifungals. The safety and efficacy of isavuconazole in children has not yet been established.

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REFERENCES

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2. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR 3rd, et al.; VITAL and FungiScope Mucormycosis Investigators. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis 2016;16:828-37. https://doi.org/10.1016/S1473-3099(16)00071-2

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency and the Therapeutic Goods Administration.