Isavuconazole

(Isavuconazonium sulfate)

Indication: [1][2][3]

- For the treatment of invasive Aspergillosis and Mucormycosis in patients 18 years and older

Dosage:

- Oral: [2][3]
  - *Loading dose:* 2 capsules (200 mg isavuconazole or 372 mg isavuconazonium) by mouth every 8 hours for 6 doses.
  - *Maintenance dose:* 2 capsules PO once daily. Start maintenance dose 12 to 24 hours after the last loading dose.
- Intravenous: [2]
  - *Loading dose:* 200 mg isavuconazole (372 mg isavuconazonium) IV every 8 hours for 6 doses.
  - *Maintenance dose:* 200 mg isavuconazole (372 mg isavuconazonium) IV once daily. Start maintenance dose 12 to 24 hours after the last loading dose.

Administration:

- Oral: [2]
  - May be administered with or without food.
  - Swallow capsules whole. Do not chew, crush, dissolve, or open the capsules.
- Nasogastric tube: [2]
  - Use the injectable formulation to obtain solution for nasogastric administration.
  - Aseptically reconstitute the contents of 1 vial with 5 mL of Sterile Water for Injection. Gently shake the vial to completely dissolved the powder.
  - Withdraw the entire contents of the vial (5 mL) using a syringe and needle.
  - Connect the syringe to the nasogastric tube to deliver the dose. Then give three 5 mL water rinses to the nasogastric tube.
  - Must be administered within 1 hour of reconstitution.
- Intravenous infusion: [2]
  - Reconstitution:
    - Aseptically reconstitute the contents of 1 vial with 5 mL of Sterile Water for Injection. Gently shake the vial to completely dissolve the powder.
    - Reconstituted solution may be stored below 25 degrees C for a maximum of 1 hour before dilution.
  - Dilution:
    - Remove 5 mL from the vial and add to 250 mL bag of either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently mix by rolling the bag. DO NOT shake.
    - Apply an in-line filter with microporous membrane pore size of 0.2 to 1.2 micron.

        - The diluted solution must be administered within 6 hours if stored at room temperature (25 degrees C). If immediately stored at 2 to 8 degrees C, the diluted solution must be administered within 24 hours of dilution. DO NOT freeze.
    - Administration:
        - Flush IV lines with 0.9% Sodium Chloride or 5% Dextrose in Water before and after administration.
        - Must be administered through a 0.2 to 1.2 micro filter.
        - Administer via IV infusion over a minimum of 1 hour. DO NOT give as a bolus injection.
- Antifungal therapy must be continued until clinical resolution of the infection, resolution of radiological signs of active disease, and elimination of predisposing factors (i.e., hyperglycemia, immunosuppression). [3]

Precautions: [2]

- Familial short QT syndrome:
    - Contraindicated for use in patients with familial short QT syndrome.
    - Isavuconazole shortens the QTc interval in a dose-related manner.
    - Familial short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias.
- Hepatotoxicity:
    - Monitor liver function tests in all patients at start of treatment and throughout the course of therapy.
    - If signs of liver disease develop during treatment, consider discontinuing therapy.
    - Use of azole antifungals, including isavuconazole, in patients with serious underlying medical conditions (e.g., hematologic malignancy) has been associated with hepatitis, cholestasis, and fatal hepatic failure.
- Infusion-related reactions:
    - Reactions have been reported with the infusion. Administer each dose over a minimum of 1 hour to reduce the risk of developing these reactions; DO NOT administer via intravenous bolus. Immediately stop the infusion if an infusion-related reaction occurs.
- Embryo-fetal toxicity:
    - May be associated with reproductive risk.
    - Advise females of reproductive potential to use effective contraception during treatment and for 28 days after the last dose.

Adverse Reactions: [2]

- *Hepatic:* abnormal liver function tests (e.g., elevated hepatic enzymes, increased bilirubin, increased gamma-glutamyltransferase), cholecystitis, cholelithiasis, hepatitis, hepatomegaly, and hepatic failure (fatal and non-fatal)
- *Cardiac:* dose-related shortening of the QTc interval, peripheral edema, chest pain, hypotension, atrial fibrillation, atrial flutter, bradycardia, palpitations, supraventricular extrasystoles, supraventricular tachycardia (SVT), ventricular extrasystoles, cardiac arrest, and thrombo-phlebitis

- *Infusion-related reactions*: chills, dizziness, dyspnea, paresthesia, hypoesthesia, hypotension, injection site reaction, and catheter thrombosis
- *Dermatologic:* rash, pruritus, alopecia, dermatitis, exfoliative dermatitis, erythema, petechiae, and urticaria
- *Gastrointestinal:* abdominal pain, anorexia, constipation, diarrhea, dyspepsia, nausea, vomiting, abdominal distension, dysgeusia, gastritis, gingivitis, and stomatitis
- *Neurologic:* headache, fatigue, insomnia, anxiety, delirium (reported as agitation, confusion, delirium, disorientation, and mental status changes), hallucinations, depression, convulsion, encephalopathy, hypoesthesia, malaise, migraine, optic neuropathy, peripheral neuropathy, somnolence, stupor, syncope, falls, vertigo, tinnitus, and tremor
- *Renal:* renal failure, hematuria, and proteinuria
- *Respiratory:* acute respiratory failure, bronchospasm, cough, dyspnea, and tachypnea
- *Musculoskeletal:* back pain, bone pain, myositis, and neck pain
- *Hematologic:* agranulocytosis, leukopenia, and pancytopenia
- *Laboratory abnormalities:* hypokalemia, hypomagnesemia, hyponatremia, hypoalbuminemia, and hypoglycemia

Drug Interactions: [2]

- CYP3A4 inhibitors and inducers:
    - Concomitant use of these drugs is contraindicated.
    - Concurrent administration with potent CYP3A4 inhibitors or inducers can significantly alter isavuconazole plasma concentrations, resulting in either toxicity or lack of efficacy.
- Substrates of CYP3A4, P-glycoprotein (P-gp), or the Organic cation transporter 2 (OCT2)
    - Isavuconazole is a moderate inhibitor of CYP3A4 and a mild inhibitor of P-gp and OCT2.
    - Concurrent use with substates of CYP3A4, P-gp, or OCT2 may result in elevated plasma concentrations of the interacting medication.
- Drugs that prolong the QT

References:

1. Central Drugs Standard Control Organization. List of new drugs approved in the year 2020 till date. Retrieved May 7, 2021. Available at on the World Wide Web at: https://cdsco.gov.in/opencms/opencms/en/Approval_new/Approved-New-Drugs/.
2. Cresemba (isavuconazonium) package insert. Northbrook, IL: Astellas Pharma US, Inc; 2021 Apr.
3. Directorate General of Health Services, MoHFW, GOI. Comprehensive Guidelines for Management of COVID-19 patients. Retrieved June 7, 2021. Available on the World Wide Web at: https://dghs.gov.in/WriteReadData/News/202105270436027770348ComprehensiveGuidelinesforManagementofCOVID-1927May2021DteGHS.pdf