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Press Release

Hikma launches Posaconazole Oral Suspension in the US

London, 3 April 2023 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces it has launched Posaconazole Oral Suspension in 40mg/mL dose. The product, launched in the US, will be the first generic on the market, broadening the choice of medicine available to doctors and patients.

Posaconazole Oral Suspension is indicated for prophylaxis of invasive Aspergillus and Candida infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy in adult and pediatric patients aged 13 years and older. Posaconazole oral suspension is also indicated for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole in adult and pediatric patients aged 13 years and older.

According to IQVIA, US sales of Posaconazole Oral Suspension, 40mg/mL were approximately $16 million in the 12 months ending January 2023.

- ENDS -

Enquiries

Hikma Pharmaceuticals PLC

Susan Ringdal
EVP, Strategic Planning and Global Affairs

+44 (0)20 7399 2760/ +44 7776 477050
uk-investors@hikma.uk.com

Steve Weiss
David Belian
US Communications and Public Affairs

+1 732 720 2830/ +1 732 788 8279
+1 732 720 2814/+1 848 254 4875
uscommunications@hikma.com

About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB-/stable S&P and BBB-/stable Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across North America, the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 8,800 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm, are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

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This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.

Important Safety Information for Posaconazole Oral Suspension, 40mg/mL:

CONTRAINDICATIONS

- **Hypersensitivity**

Posaconazole is contraindicated in persons with known hypersensitivity to posaconazole or other azole antifungal agents.

- **Use With Sirolimus**

Concomitant administration of posaconazole with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity.

- **QT Prolongation With Concomitant Use With CYP3A4 Substrates**

Posaconazole is contraindicated with CYP3A4 substrates that prolong the QT interval. Concomitant administration of posaconazole with the CYP3A4 substrates pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and cases of *torsades de pointes*.

- **HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4**

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis.

- **Use With Ergot Alkaloids**

Posaconazole may increase the plasma concentrations of ergot alkaloids, which may lead to ergotism.

- **Use With Venetoclax**

Coadministration with venetoclax at initiation and at the ramp-up phase is contraindicated in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) due to the potential for increased risk of tumor lysis syndrome (TLS).

WARNINGS AND PRECAUTIONS

- **Calcineurin-Inhibitor Drug Interactions**

Concomitant administration with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin-inhibitors.

Nephrotoxicity and leukoencephalopathy (including deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine or tacrolimus concentrations. Frequent monitoring of tacrolimus or cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus or cyclosporine dose adjusted accordingly.

- **Arrhythmias and QT Prolongation**

Some azoles, including posaconazole, have been associated with prolongation of the QT interval on the electrocardiogram. In addition, cases of *torsades de pointes* have been reported in patients taking posaconazole.

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4.

- **Electrolyte Disturbances**

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.

- **Hepatic Toxicity**

Hepatic reactions have been reported in clinical trials. Cases of more severe hepatic reactions, including cholestasis or hepatic failure (including deaths), have been reported in patients with serious underlying medical conditions during treatment with posaconazole. These severe hepatic reactions were seen primarily in clinical trial subjects receiving 800 mg posaconazole oral suspension daily (400 mg BID or 200 mg QID).

Liver function should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during posaconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of posaconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to posaconazole.

- **Renal Impairment**

Patients with severe renal impairment should be monitored closely for breakthrough fungal infections.

- **Midazolam Toxicity**

Concomitant administration with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Patients must be monitored closely for adverse effects associated with high plasma concentrations of midazolam, and benzodiazepine receptor antagonists must be available to reverse these effects.

- **Vincristine Toxicity**

Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

- **Breakthrough Fungal Infections**

Patients with severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections when receiving posaconazole.

- **Venetoclax Toxicity**

Concomitant administration may increase venetoclax toxicities, including the risk of TLS, neutropenia and serious infections. In patients with CLL/SLL, administration during the initiation and ramp-up phase of venetoclax is contraindicated. Refer to the venetoclax labeling for safety monitoring and dose reduction in the steady daily dosing phase in CLL/SLL patients.

For patients with acute myeloid leukemia (AML), dose reduction and safety monitoring are recommended across all dosing phases when coadministering posaconazole with venetoclax. See the Full Prescribing Information for venetoclax for dosing instructions.

ADVERSE REACTIONS

The following serious and otherwise important adverse reactions are discussed in detail in the Full Prescribing Information for posaconazole oral suspension:

- Hypersensitivity
- Arrhythmias and QT Prolongation
- Hepatic Toxicity

In prophylaxis clinical trials, the most frequently reported adverse reactions (>30%) were fever, diarrhea and nausea. In studies of HIV-infected patients with oropharyngeal *Candida* (OPC) and refractory OPC (rOPC), the most common adverse reactions were fever, diarrhea, nausea, headache, vomiting and coughing. Adverse reactions were reported more frequently in study patients with rOPC.

Advise patients to inform their physician immediately if they develop severe diarrhea or vomiting, if they notice swelling in an arm or leg or if they experience shortness of breath.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of posaconazole cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

DRUG INTERACTIONS

Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections.

Posaconazole is also a strong inhibitor of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole.

- **Immunosuppressants Metabolized by CYP3A4**

Sirolimus: Posaconazole is contraindicated with sirolimus.

Tacrolimus: At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly.

Cyclosporine: Posaconazole has been shown to increase cyclosporine whole blood concentrations in heart transplant patients upon initiation of posaconazole treatment. Reduce the cyclosporine dose to approximately three-fourths of the original dose upon initiation of posaconazole treatment. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly.

- **CPY3A4 Substrates**

Concomitant administration of posaconazole with CYP3A4 substrates is contraindicated.

- **HMG-CoA Reductase Inhibitors (Statins) Primarily Metabolized Through CYP3A4**

Posaconazole is contraindicated with HMG-CoA reductase inhibitors primarily metabolized through CYP3A4.

- **Ergot Alkaloids**

Posaconazole is contraindicated with ergot alkaloids.

- **Benzodiazepines Metabolized by CYP3A4**

Concomitant administration of posaconazole with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant use of posaconazole and other benzodiazepines metabolized by CYP3A4 could result in increased plasma concentrations of these benzodiazepines. Patients must be monitored closely for adverse effects associated with high plasma concentrations of benzodiazepines metabolized by CYP3A4, and benzodiazepine receptor antagonists must be available to reverse these effects.

- **Anti-HIV Drugs**

Efavirenz: Avoid concomitant use of efavirenz with posaconazole unless the benefit outweighs the risks.

Ritonavir and Atazanavir: Monitor patients frequently for adverse effects and toxicity of ritonavir and atazanavir during coadministration with posaconazole.

Fosamprenavir: If concomitant administration of fosamprenavir with posaconazole is required, close monitoring for breakthrough fungal infections is recommended.

- **Rifabutin**

Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. If concomitant administration is required, monitor the patient closely for breakthrough fungal infections. Frequent monitoring of full blood counts and adverse reactions due to increased rifabutin plasma concentrations is also recommended.

- **Phenytoin**

Concomitant use of posaconazole and phenytoin should be avoided unless the benefit outweighs the risk. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. Monitor phenytoin concentrations frequently and consider reducing the dose of phenytoin.

- **Gastric Acid Suppressors/Neutralizers**

Avoid concomitant use of cimetidine and esomeprazole with posaconazole oral suspension unless the benefit outweighs the risks. If concomitant administration is required, monitor patient closely for breakthrough fungal infections.

- **Vinca Alkaloids**

Concomitant administrations of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions. Posaconazole may increase the plasma concentrations of vinca alkaloids, which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

- **Calcium Channel Blockers Metabolized by CYP3A4**

Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during coadministration with posaconazole. Dose reduction of calcium channel blockers may be needed.

- **Digoxin**

Monitoring of digoxin plasma concentrations is recommended during coadministration with posaconazole.

- **Gastrointestinal Motility Agents**

Monitor patients closely for breakthrough fungal infections during concomitant administration with metoclopramide. No dosage adjustment of posaconazole oral suspension is required when loperamide and posaconazole oral suspension are used concomitantly.

- **Glipizide**

Monitor glucose concentrations when posaconazole and glipizide are concomitantly used.

- **Venetoclax**

Concomitant use of venetoclax with posaconazole increases venetoclax C_{max} and $AUC_{0\text{-}INF}$, which may increase venetoclax toxicities. See the Full Prescribing Information for venetoclax for more information on dosing instructions and the extent of increase in venetoclax exposure.

USE IN SPECIFIC POPULATIONS

- **Pregnancy**

Based on findings from animal data, posaconazole may cause fetal harm when administered to pregnant women.

- **Lactation**

There are no data on the presence of posaconazole in human milk, the effects on the breastfed infant or the effects on milk production. Posaconazole is excreted in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for posaconazole and any potential adverse effects on the breastfed child from posaconazole or from the underlying maternal condition.

- **Pediatric Use**

The safety and effectiveness of posaconazole in pediatric patients younger than 13 years have not been established.

- **Geriatric Use**

No overall differences in pharmacokinetics and safety were observed between elderly and young subjects during clinical trials, but greater sensitivity of some older individuals cannot be ruled out.

- **Renal Impairment**

Patients with severe renal impairment should be monitored closely for breakthrough fungal infections.

- **Weight**

Patients weighing >120 kg should be monitored closely for breakthrough fungal infections.

DOSAGE AND ADMINISTRATION

Posaconazole oral suspension is not substitutable with posaconazole delayed-release tablets or posaconazole powder for delayed-release oral suspension due to the differences in dosing of each formulation.

Administer with a full meal (or liquid nutritional supplement or acidic carbonated beverage in patients who cannot eat a full meal). For details, see the Full Prescribing Information for posaconazole oral suspension.

Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. Monitor patients who require these drugs closely for breakthrough fungal infections.

For more information, please see the Full Prescribing Information, including the Boxed Warning.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit https://www.fda.gov/medwatch or call 1-800-FDA-1088.

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