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Press Release

Hikma launches Micafungin for Injection

London, 12 October 2021 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces it launched Micafungin for Injection through its US affiliate, Hikma Pharmaceuticals USA Inc. The company has launched 50mg and 100mg doses.

Micafungin for Injection is indicated for:

- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses in adult and pediatric patients 4 months of age and older.
- Treatment of Esophageal Candidiasis in adult and pediatric patients 4 months of age and older.
- Prophylaxis of *Candida* Infections in adult and pediatric patients 4 months of age and older undergoing hematopoietic stem cell transplantation.

According to IQVIA, US sales of Micafungin for Injection, 50mg and 100mg were approximately $132 million in the 12 months ending August 2021.

Hikma is the third largest US supplier of generic injectable medicines by volume, with a growing portfolio of over 100 products. Today one in every six injectable generic medicines used in US hospitals is a Hikma product.

- ENDS -

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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 the United States (US), 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 8,600 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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Important Safety Information for Micafungin for Injection, 50mg and 100mg:

CONTRAINDICATIONS

Micafungin for injection is contraindicated in persons with known hypersensitivity to micafungin, any component of micafungin for injection, or other echinocandins.

WARNINGS & PRECAUTIONS

- **Hypersensitivity Reactions –** Isolated cases of serious hypersensitivity (anaphylaxis and anaphylactoid) reactions (including shock) have been reported in patients receiving micafungin for injection. If these reactions occur, micafungin for injection infusion should be discontinued and appropriate treatment administered.
- **Hematological Effects –** Acute intravascular hemolysis and hemoglobinuria was seen in a healthy volunteer during infusion of micafungin for injection (200 mg) and oral prednisolone (20 mg). Cases of significant hemolysis and hemolytic anemia have also been reported in patients treated with micafungin for injection. Patients who develop clinical or laboratory evidence of hemolysis or hemolytic anemia during micafungin for injection therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing micafungin for injection therapy.
- **Hepatic Effects –** Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with micafungin for injection. In some patients with serious underlying conditions who were receiving micafungin for injection along with multiple concomitant medications, clinical hepatic abnormalities have occurred, and isolated cases of significant hepatic impairment, hepatitis, and hepatic failure have been reported. Patients who develop abnormal liver function tests during micafungin for injection therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/ benefit of continuing micafungin for injection therapy.
- **Renal Effects –** Elevations in BUN and creatinine, and isolated cases of significant renal impairment or acute renal failure have been reported in patients who received micafungin for injection. In fluconazole-controlled trials, the incidence of drug-related renal adverse reactions was 0.4% for micafungin for injection-treated patients and 0.5% for fluconazole-treated patients. Patients who develop abnormal renal function tests during micafungin for injection therapy should be monitored for evidence of worsening renal function.
- **Infusion and Injection Site Reactions –** Possible histamine-mediated symptoms have been reported with micafungin for injection, including rash, pruritus, facial swelling, and vasodilatation. Slow the infusion rate if infusion reaction occurs. Injection site reactions, including phlebitis and thrombophlebitis have been reported, at micafungin for injection doses of 50 to 150 mg/day. These reactions tended to occur more often in patients receiving micafungin for injection via peripheral intravenous administration.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Hematological Effects *[see Warnings and Precautions (5.2)]*
- Hepatic Effects *[see Warnings and Precautions (5.3)]*
- Renal Effects *[see Warnings and Precautions (5.4)]*
- Infusion and Injection Site Reactions *[see Warnings and Precautions (5.5)]*

Clinical Trials Experience
The overall safety of micafungin for injection was assessed in 520 health volunteers and 3,227 adult and pediatric patients who received single or multiple doses of micafungin for injection across 46 clinical trials, including the invasive candidiasis, esophageal candidiasis and prophylaxis trials. The doses of micafungin for injection administered included doses above and below the recommended doses and ranged from 0.75 mg/kg to 10 mg/kg in pediatric patients and 12.5 mg to 150 mg/day or greater in adult patients.

Clinical Trials Experience in Adults
In clinical trials with micafungin for injection, 2,497/2,748 (91%) adult patients experienced at least one adverse reaction. Refer to the tables in the package insert:

- Table 3: Selected Adverse Reactions in Adult Patients with Candidemia and Other Candida Infections
- Table 4: Selected Adverse Reactions in Adult Patients with Esophageal Candidiasis
- Table 5: Selected Adverse Reactions in Adult Patients During Prophylaxis of Candida Infection in Hematopoietic

Stem Cell Transplant Recipients

Patient base: all randomized patients who received at least 1 dose of trial drug. Other selected adverse reactions reported at less than 5% in adult clinical trials are listed below:
Blood and lymphatic system disorders: coagulopathy, pancytopenia, thrombotic thrombocytopenic purpura
Cardiac disorders: cardiac arrest, myocardial infarction, pericardial effusion
General disorders and administration site conditions: infusion reaction, injection site thrombosis
Hepatobiliary disorders: hepatocellular damage, hepatomegaly, jaundice, hepatic failure
Immune disorders: hypersensitivity, anaphylactic reaction
Metabolism and nutrition disorders: hypernatremia, hypokalemia
Nervous system disorders: convulsions, encephalopathy, intracranial hemorrhage
Psychiatric disorders: delirium
Skin and subcutaneous tissue disorders: urticaria

Clinical Trials Experience in Pediatric Patients
The safety of micafungin for injection was assessed in 479 pediatric patients through 16 years of age who received at least one dose of micafungin for injection across 11 clinical trials. A total of 246 patients received at least one dose of micafungin for injection ranging from 2 to 10 mg/kg.

Overall, 439/479 (92%) patients experienced at least one adverse reaction. Refer to the table in the package insert:

- Table 6: Selected Adverse Reactions in Pediatric Patients with Candidemia and Other *Candida* Infections (C/IC), and in Hematopoietic Stem-Cell Recipients During Prophylaxis of *Candida* Infections

Other clinically significant adverse reactions reported at less than 15% in pediatric clinical trials are listed below:
Hepatobiliary disorders: hyperbilirubinemia
Investigations: liver tests abnormal
Renal Disorders: renal failure

Postmarketing Experience
The following adverse reactions have been identified during the post-approval use of micafungin for injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: disseminated intravascular coagulation
Hepatobiliary disorders: hepatic disorder
Renal and urinary disorders: renal impairment
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis
Vascular disorders: shock

DRUG INTERACTIONS

Effect of Other Drugs on Micafungin for Injection
CYP3A4, CYP2C9 and CYP2C19 Inhibitors
Co-administration of micafungin for injection with cyclosporine, itraconazole, voriconazole and fluconazole did not alter the pharmacokinetics of micafungin for injection.

CYP2C19 and CYP3A4 Inducer
Co-administration of micafungin for injection with rifampin and ritonavir did not alter the pharmacokinetics of micafungin for injection.

Co-administration of Micafungin for Injection with Other Drugs
Co-administration of micafungin for injection with mycophenolate mofetil (MMF), amphotericin B, tacrolimus, prednisolone, sirolimus and nifedipine did not alter the pharmacokinetics of micafungin for injection.

Effect of Micafungin for Injection on Other Drugs
CYP3A4 Substrates
There was no effect of single or multiple doses of micafungin for injection on cyclosporine, tacrolimus, prednisolone, voriconazole and fluconazole pharmacokinetics.

Patients receiving sirolimus, nifedipine, and itraconazole in combination with micafungin for injection should be monitored for sirolimus, nifedipine, and itraconazole toxicity and the sirolimus, nifedipine, and itraconazole dosage should be reduced if necessary.

UDP-Glycosyltransferase Substrate
Co-administration of mycophenolate mofetil (MMF) with micafungin for injection did not alter the pharmacokinetics of MMF.

USE IN SPECIFIC POPULATIONS

Pregnancy
Based on findings from animal studies, micafungin for injection may cause fetal harm when administered to a pregnant woman. There is insufficient human data on the use of micafungin for injection in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Advise pregnant women of the risk to the fetus.

Lactation
There are no data on the presence of micafungin in human milk, the effects on the breast-fed infant or the effects on milk production. Micafungin was present in the milk of lactating rats following intravenous administration. 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 micafungin for injection, and any potential adverse effects on the breast-fed child from micafungin for injection, or from the underlying maternal condition.

Pediatric Use
Pediatric Patients 4 Months of Age and Older
The safety and effectiveness of micafungin for injection for the treatment of esophageal candidiasis, candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses, esophageal candidiasis, and for prophylaxis of *Candida* infections in patients undergoing HSCT have been established in pediatric patients 4 months of age and older.

Pediatric Patients Younger than 4 Months of Age
The safety and effectiveness of micafungin for injection have ***not*** been established for the treatment of candidemia ***with*** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age.

The safety and effectiveness of micafungin for injection in pediatric patients younger than 4 months of age have not been established for the:
- Treatment of esophageal candidiasis
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation

Geriatric Use
A total of 418 subjects in clinical studies of micafungin for injection were 65 years of age and older, and 124 subjects were 75 years of age and older. No overall differences in safety and effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The exposure and disposition of a 50 mg micafungin for injection dose administered as a single 1-hour infusion to 10 healthy subjects aged 66 to 78 years were not significantly different from those in 10 healthy subjects aged 20 to 24 years. No dose adjustment is necessary for the elderly.

Use in Patients with Renal Impairment
Micafungin for injection does not require dose adjustment in patients with renal impairment. Supplementary dosing should not be required following hemodialysis.

Use in Patients with Hepatic Impairment
Dose adjustment of micafungin for injection is not required in patients with mild, moderate, or severe hepatic impairment.

Race and Gender

No dose adjustment of micafungin for injection is required based on gender or race. No notable differences among white, black, and Hispanic subjects were seen.

DOSAGE AND ADMINISTRATION

Dosage for Adults
The recommended dosage for adult patients based on indications are shown in Table 1 in the package insert.

Dosage for Pediatric Patients 4 Months and Older
The recommended dosage for pediatric patients 4 months of age and older based on indication and weight are shown in Table 2 in the package insert.

Directions for Reconstitution, Dilution, and Preparation
Do not mix or co-infuse micafungin for injection with other medications. Micafungin for injection has been shown to precipitate when mixed directly with a number of other commonly used medications. Please read this entire section carefully before beginning reconstitution.

Reconstitution
Reconstitute micafungin for injection vials by aseptically adding 5 mL of one of the following compatible solutions:
- 0.9% Sodium Chloride Injection, USP (without a bacteriostatic agent)
- 5% Dextrose Injection, USP

To minimize excessive foaming, gently dissolve the micafungin for injection powder by swirling the vial. *Do not vigorously shake the vial*. Visually inspect the vial for particulate matter.

Micafungin for injection 50 mg vial: after reconstitution each mL contains 10 mg of micafungin.
Micafungin for injection 100 mg vial: after reconstitution each mL contains 20 mg of micafungin.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if there is any evidence of precipitation or foreign matter. Aseptic technique must be strictly observed in all handling since no preservative or bacteriostatic agent is present in micafungin for injection or in the materials specified for reconstitution and dilution.

The reconstituted product should be protected from light and may be stored in the original vial for up to 24 hours at room temperature, 25°C (77°F).

Dilution and Preparation
The diluted solution should be protected from light. It is not necessary to cover the infusion drip chamber or the tubing.

Adult Patients:
1. Add the appropriate volume of reconstituted micafungin for injection into 100 mL of 0.9% Sodium Chloride Injection, USP or 100 mL of 5% Dextrose Injection, USP.
2. Appropriately label the bag.

Pediatric Patients:
1. Calculate the total micafungin for injection dose in milligrams (mg) by multiplying the recommended pediatric dose (mg/ kg) for a given indication *[see Table 2 in the package insert]* and the weight of the patient in kilograms (kg).
2. To calculate the volume (mL) of drug needed, divide the calculated dose (mg) from step 1 by the final concentration of the selected reconstituted vial(s) (either 10 mg/mL for the 50 mg vial **or** 20 mg/mL for the 100 mg vial).
3. Withdraw the calculated volume (mL) of drug needed from the selected concentration and size of reconstituted micafungin for injection vial(s) used in Step 2 (ensure the selected concentration and vial size used to calculate the dose is also used to prepare the infusion).
4. Add the withdrawn volume of drug (step 3) to a 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP intravenous infusion bag or syringe. Ensure that the final concentration of the solution is between 0.5 mg/mL to 4 mg/ mL. To decrease the risk of infusion reactions, concentrations above 1.5 mg/mL should be administered via central catheter.

5. Appropriately label the infusion bag or syringe. For concentrations above 1.5 mg/mL, if required, label to specifically warn to administer the solution via central catheter.

The diluted infusion bag should be protected from light and may be stored for up to 24 hours at room temperature, 25°C (77°F).

Micafungin for injection is preservative-free. Discard partially used vials.

Infusion Volume and Duration
Administer micafungin for injection by intravenous infusion only. Infuse over one hour. More rapid infusions may result in more frequent histamine-mediated reactions. Flush an existing intravenous line with 0.9% Sodium Chloride Injection, USP, prior to infusion of micafungin for injection.

Pediatric Patients
Micafungin for injection should be infused over one hour. To decrease the risk of infusion reactions, concentrations above 1.5 mg/mL should be administered via central catheter.

DRUG ABUSE AND DEPENDENCE

There has been no evidence of either psychological or physical dependence or withdrawal or rebound effects with micafungin for injection.

OVERDOSAGE

Micafungin for injection is highly protein bound and, therefore, is not dialyzable. No cases of micafungin for injection overdosage have been reported. Repeated daily doses up to 8 mg/kg (maximum total dose of 896 mg) in adult patients, up to 6 mg/kg in pediatric patients 4 months of age and older, and up to 10 mg/kg in pediatric patients younger than 4 months of age have been administered in clinical trials with no reported dose-limiting toxicity.

INDICATIONS AND USAGE

Micafungin for Injection is indicated for:
- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses in adult and pediatric patients 4 months of age and older.
- Treatment of Esophageal Candidiasis in adult and pediatric patients 4 months of age and older.
- Prophylaxis of *Candida* Infections in adult and pediatric patients 4 months of age and older undergoing hematopoietic stem cell transplantation.

Limitations of Use
- Micafungin for injection has not been adequately studied in patients with endocarditis, osteomyelitis and meningoencephalitis due to *Candida.*
- The efficacy of micafungin for injection against infections caused by fungi other than *Candida* has not been established.

Additional pediatric use information is approved for Astellas Pharma US, Inc.'s Mycamine® (micafungin for injection). However, due Astellas Pharma US, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

HOW SUPPLIED/STORAGE AND HANDLING

Micafungin for Injection is supplied as a sterile, white lyophilized powder for reconstitution for intravenous infusion, and is available in the following packaging configurations:

- NDC 0143-9361-01, 50 mg Single-dose vials, sealed with a blue flip-off cap, packaged individually
- NDC 0143-9362-01, 100 mg Single-dose vials, sealed with a red flip-off cap, packaged individually

Storage

Unopened vials of lyophilized material must be stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Store the reconstituted product at 25°C (77°F). Store the diluted solution at 25°C (77°F). Protect from light.

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA, Inc. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**. For Product Inquiry call 1-877-845-0689.

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