Press Release

Hikma launches Foscarnet Sodium Injection, in the US

London, 23 September 2024 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Foscarnet Sodium Injection, in a 6000mg/250mL bottle in the US. The product is indicated for:

- the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). Combination therapy with foscarnet sodium and ganciclovir is indicated for patients who have relapsed after monotherapy with either drug
- the treatment of acyclovir-resistant mucocutaneous HSV infections in immunocompromised patients

According to IQVIA, US sales of Foscarnet Sodium Injection, 6000mg/250mL, were approximately $19 million in the 12 months ending July 2024.

Hikma is a top three supplier of generic injectable medicines by volume in the US[1], with a growing portfolio of more than 160 products. We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that enhance patient care.

- ENDS –

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.

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

Hikma helps put better health within reach every day for millions of people around the world. For more than 45 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 North America, the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge

[1] Source: IQVIA MAT July 2024, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

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 9,100 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

Important Safety Information for Foscarnet Sodium Injection, 6000mg/250mL:

Please see package insert for referenced section/section numbering, where appropriate.

BOXED WARNING

WARNING

RENAL IMPAIRMENT IS THE MAJOR TOXICITY OF FOSCARNET SODIUM INJECTION. FREQUENT MONITORING OF SERUM CREATININE, WITH DOSE ADJUSTMENT FOR CHANGES IN RENAL FUNCTION, AND ADEQUATE HYDRATION WITH ADMINISTRATION OF FOSCARNET SODIUM INJECTION IS IMPERATIVE. (See ADMINISTRATION section; Hydration.)

SEIZURES, RELATED TO ALTERATIONS IN PLASMA MINERALS AND ELECTROLYTES, HAVE BEEN ASSOCIATED WITH FOSCARNET SODIUM INJECTION TREATMENT. THEREFORE, PATIENTS MUST BE CAREFULLY MONITORED FOR SUCH CHANGES AND THEIR POTENTIAL SEQUELAE. MINERAL AND ELECTROLYTE SUPPLEMENTATION MAY BE REQUIRED.

FOSCARNET SODIUM INJECTION IS INDICATED FOR USE ONLY IN IMMUNOCOMPROMISED PATIENTS WITH CMV RETINITIS AND MUCOCUTANEOUS ACYCLOVIR-RESISTANT HSV INFECTIONS. (See INDICATIONS section).

CONTRAINDICATIONS

Foscarnet sodium injection is contraindicated in patients with clinically significant hypersensitivity to foscarnet sodium.

WARNINGS & PRECAUTIONS

- **Renal Impairment –** THE MAJOR TOXICITY OF FOSCARNET SODIUM IS RENAL IMPAIRMENT. Renal impairment is most likely to become clinically evident during the second week of induction therapy, but may occur at any time during foscarnet sodium treatment.
- **Mineral and Electrolyte Abnormalities –** Foscarnet sodium has been associated with changes in serum electrolytes including hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, and hypokalemia. Foscarnet sodium may also be associated with a dose-related decrease in ionized serum calcium which may not be reflected in total serum calcium.
- **Seizures –** Seizures related to mineral and electrolyte abnormalities have been associated with foscarnet sodium treatment. Several cases of seizures were associated with death. Cases of status epilepticus have been reported. Risk factors associated with seizures included impaired baseline renal function, low total serum calcium, and underlying CNS conditions.
- **Hypersensitivity –** Serious acute hypersensitivity reactions (e.g., anaphylactic shock, urticaria, angioedema) have been reported postmarketing in patients receiving foscarnet sodium.
- **QT prolongation and torsade de pointes –** Foscarnet sodium has been associated with prolongation of the QT interval, an ECG abnormality that has been associated with torsades de pointes, which has been reported during postmarketing surveillance for foscarnet sodium.
- **Irritation –** Care must be taken to infuse solutions containing foscarnet sodium only into veins with adequate blood flow to permit rapid dilution and distribution to avoid local irritation.
- **Sodium Content –** Due to the sodium content of foscarnet sodium, avoid foscarnet sodium use when intravenous infusion of a large amount of sodium or water may not be tolerated (e.g. in patients with cardiomyopathy). Foscarnet sodium should also be avoided in patients on a controlled sodium diet.
- **Hematopoietic System –** Anemia has been reported in 33% of patients receiving foscarnet sodium in controlled studies. Granulocytopenia has been reported in 17% of patients receiving foscarnet sodium in controlled studies; however, only 1% (2/189) were terminated from these studies because of neutropenia.

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ADVERSE REACTIONS

Clinical Trials

In five controlled U.S. clinical trials the most frequently reported adverse events in patients with AIDS and CMV retinitis are shown in Table 9 of the Package Insert. From the same controlled studies, adverse events categorized by investigator as “severe” are shown in Table 10 of the Package Insert.

From the five initial U.S. controlled trials of foscarnet sodium injection, the following list of adverse events has been compiled regardless of causal relationship to foscarnet sodium. Evaluation of these reports was difficult because of the diverse manifestations of the underlying disease and because most patients received numerous concomitant medications.

Incidence of 5% or Greater

Body as a Whole: fever, fatigue, rigors, asthenia, malaise, pain, infection, sepsis, death
Central and Peripheral Nervous System: headache, paresthesia, dizziness, involuntary muscle contractions, hypoesthesia, neuropathy, seizures including grand mal seizures
Gastrointestinal System: anorexia, nausea, diarrhea, vomiting, abdominal pain
Hematologic: anemia, granulocytopenia, leukopenia, neutropenia
Metabolic and Nutritional: mineral and electrolyte imbalances including hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia
Psychiatric: depression, confusion, anxiety
Respiratory System: coughing, dyspnea
Skin and Appendages: rash, increased sweating
Urinary System: alterations in renal function including increased serum creatinine, decreased creatinine clearance, and abnormal renal function
Special Senses: vision abnormalities

Incidence between 1% and 5%

Application Site: injection site pain, injection site inflammation
Body as a Whole: back pain, chest pain (including reports of transient chest pain as part of infusion reactions), edema, influenza-like symptoms, bacterial infections, moniliasis, fungal infections, abscess
Cardiovascular: hypertension, palpitations, ECG abnormalities including sinus tachycardia, first degree AV block and non-specific ST-T segment changes, hypotension, flushing, cerebrovascular disorder
Central and Peripheral Nervous System: tremor, ataxia, dementia, stupor, generalized spasms, sensory disturbances, meningitis, aphasia, abnormal coordination, leg cramps, EEG abnormalities
Gastrointestinal: constipation, dysphagia, dyspepsia, rectal hemorrhage, dry mouth, melena, flatulence, ulcerative stomatitis, pancreatitis
Hematologic: thrombocytopenia, platelet abnormalities, thrombosis, white blood cell abnormalities, lymphadenopathy
Liver and Biliary: abnormal A-G ratio, abnormal hepatic function, increased SGPT, increased SGOT
Metabolic and Nutritional: hyponatremia, decreased weight, increased alkaline phosphatase, increased LDH, increased BUN, acidosis, cachexia, thirst
Musculo-Skeletal: arthralgia, myalgia
Neoplasms: lymphoma-like disorder, sarcoma
Psychiatric: insomnia, somnolence, nervousness, amnesia, agitation, aggressive reaction, hallucination
Respiratory System: pneumonia, sinusitis, pharyngitis, rhinitis, respiratory disorders, respiratory insufficiency, pulmonary infiltration, stridor, pneumothorax, hemoptysis, bronchospasm
Skin and Appendages: pruritus, skin ulceration, seborrhea, erythematous rash, maculopapular rash, skin discoloration
Special Senses: taste perversions, eye abnormalities, eye pain, conjunctivitis
Urinary System: albuminuria, dysuria, polyuria, urethral disorder, urinary retention, urinary tract infections, acute renal failure, nocturia, facial edema

Incidence less than 1%

Selected adverse events occurring at a rate of less than 1% in the five initial U.S. controlled clinical trials of foscarnet sodium include: syndrome of inappropriate antidiuretic hormone secretion, pancytopenia, hematuria, dehydration, hypoproteinemia, increases in amylase and creatinine phosphokinase, cardiac arrest, coma, and other cardiovascular and neurologic complications.

Selected adverse event data from the Foscarnet vs. Ganciclovir CMV Retinitis Trial (FGCRT), performed

by the Studies of the Ocular Complications of AIDS (SOCA) Research Group, are shown in Table 11 of the Package Insert. Selected adverse events from ACTG Study 228 (CRRT) comparing combination therapy with foscarnet sodium injection or ganciclovir monotherapy are shown in Table 12 of the Package Insert.

Post-marketing
Adverse events that have been reported in post-marketing surveillance include: administration site extravasation, localized edema, hypersensitivity reactions (including anaphylactic shock, urticaria and angioedema), gastrointestinal hemorrhage, increased lipase, glomerulonephritis, nephrotic syndrome, proteinuria, status epilepticus, ventricular arrhythmia, prolongation of QT interval, torsade de pointes, gamma GT increased, diabetes insipidus (usually nephrogenic), renal calculus, Fanconi syndrome acquired, renal tubular acidosis, renal tubular necrosis, crystal-induced nephropathy, hypercalcemia, hypernatremia, esophageal ulceration and muscle disorders including myopathy, myositis, muscle weakness and rare cases of rhabdomyolysis. Cases of vesiculobullous eruptions including erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome have been reported. In most cases, patients were taking other medications that have been associated with toxic epidermal necrolysis or Stevens-Johnson syndrome.

DRUG INTERACTIONS

A possible drug interaction of foscarnet sodium and intravenous pentamidine has been described. Concomitant treatment of four patients in the United Kingdom with foscarnet sodium and intravenous pentamidine may have caused hypocalcemia; one patient died with severe hypocalcemia. Toxicity associated with concomitant use of aerosolized pentamidine has not been reported. Because foscarnet can reduce serum levels of ionized calcium, extreme caution is advised when used concurrently with other drugs known to influence serum calcium levels (e.g., intravenous pentamidine). Renal impairment and symptomatic hypocalcemia have been observed during concurrent treatment with foscarnet and intravenous pentamidine.

Because of foscarnet's tendency to cause renal impairment, the use of foscarnet sodium should be avoided in combination with potentially nephrotoxic drugs such as aminoglycosides, amphotericin B, cyclosporine, acyclovir, methotrexate, tacrolimus and intravenous pentamidine (see above) unless the potential benefits outweigh the risks to the patient.

When diuretics are indicated, thiazides are recommended over loop diuretics because the latter inhibit renal tubular secretion, and may impair elimination of foscarnet, potentially leading to toxicity.

Abnormal renal function has been observed in clinical practice during the use of foscarnet sodium and ritonavir, or foscarnet sodium, ritonavir, and saquinavir.

Because of the risk of QT prolongation and the potential for torsades de pointes, the use of foscarnet sodium should be avoided in combination with agents known to prolong the QT interval including Class IA (e.g., quinidine or procainamide) or Class III (e.g., dofetilide, amiodarone, sotalol) antiarrhythmic agents, phenothiazines, tricyclic antidepressants, and certain macrolides and fluoroquinolones.

USE IN SPECIFIC POPULATIONS

Pregnancy
There are no adequate and well-controlled studies of foscarnet sodium in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether foscarnet sodium is excreted in human milk; however, in lactating rats administered 75 mg/kg, foscarnet sodium was excreted in maternal milk at concentrations three times higher than peak maternal blood concentrations. Because of the potential for serious adverse events in nursing infants, a decision should be made whether to discontinue nursing or discontinue drug, taking into consideration the importance of the drug to the mother. The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

Pediatric Use
The safety and effectiveness of foscarnet sodium in pediatric patients have not been established. Foscarnet sodium is deposited in teeth and bone and deposition is greater in young and growing animals. Foscarnet sodium has been demonstrated to adversely affect development of tooth enamel in mice and rats. The effects of this deposition on skeletal development have not been studied.

Since deposition in human bone has also been shown to occur, it is likely that it does so to a greater degree in developing bone in pediatric patients. Administration to pediatric patients should be undertaken only after careful evaluation and only if the potential benefits for treatment outweigh the risks.

Geriatric Use
No studies of the efficacy or safety of foscarnet sodium in persons 65 years of age or older have been conducted. However, foscarnet sodium has been used in patients age 65 years of age and older. The pattern of adverse events seen in these patients is consistent across all age groups. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

DOSAGE AND ADMINISTRATION

CAUTION – DO NOT ADMINISTER FOSCARNET SODIUM BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF FOSCARNET SODIUM MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS. CARE SHOULD BE TAKEN TO AVOID UNINTENTIONAL OVERDOSE BY CAREFULLY CONTROLLING THE RATE OF INFUSION. THEREFORE, AN INFUSION PUMP MUST BE USED. IN SPITE OF THE USE OF AN INFUSION PUMP, OVERDOSES HAVE OCCURRED.

Instructions for Administration and Preparation
Foscarnet sodium is administered by controlled intravenous infusion, either by using a central venous line or by using a peripheral vein. The rate of infusion must be no more than 1 mg/kg/minute. An individualized dose of foscarnet sodium should be calculated on the basis of body weight (mg/kg), renal function, indication of use and dosing frequency.

Hydration
Hydration may reduce the risk of nephrotoxicity. Clinically dehydrated patients should have their condition corrected before initiating foscarnet sodium therapy. Hydration fluid may need to be decreased if clinically warranted. Oral rehydration with similar regimens may be considered in certain patients. After the first dose, the hydration fluid should be administered concurrently with each infusion of foscarnet sodium.

Compatibility With Other Solutions/Drugs
Other drugs and supplements can be administered to a patient receiving foscarnet sodium. However, care must be taken to ensure that foscarnet sodium is only administered with normal saline or 5% dextrose solution and that no other drug or supplement is administered concurrently via the same catheter.

Foscarnet has been reported to be chemically incompatible with 30% dextrose, amphotericin B, and solutions containing calcium such as Ringer's lactate and TPN. Physical incompatibility with other IV drugs has also been reported including acyclovir sodium, ganciclovir, trimetrexate glucuronate, pentamidine isethionate, vancomycin, trimethoprim/sulfamethoxazole, diazepam, midazolam, digoxin, phenytoin, leucovorin, and prochlorperazine. Because of foscarnet's chelating properties, a precipitate can potentially occur when divalent cations are administered concurrently in the same catheter.

Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored or contain particulate matter should not be used.

Accidental Exposure
Accidental skin and eye contact with foscarnet sodium solution may cause local irritation and burning sensation. If accidental contact occurs, the exposed area should be flushed with water.

THE RECOMMENDED DOSAGE, FREQUENCY, OR INFUSION RATES SHOULD NOT BE EXCEEDED. ALL DOSES MUST BE INDIVIDUALIZED FOR PATIENTS' RENAL FUNCTION.

Induction Treatment
The recommended initial dose of foscarnet sodium for patients with normal renal function is:

- For CMV retinitis patients, either 90 mg/kg (1-1/2 to 2 hour infusion) every twelve hours or 60 mg/kg (minimum one hour infusion) every eight hours over 2-3 weeks depending on clinical response.
- For acyclovir-resistant HSV patients, 40 mg/kg (minimum one hour infusion) either every 8 or 12 hours for 2-3

weeks or until healed.

Maintenance Treatment
Following induction treatment the recommended maintenance dose of foscarnet sodium for CMV retinitis is 90 mg/kg/day to 120 mg/kg/day given as an intravenous infusion over 2 hours. Because the superiority of the 120 mg/kg/day has not been established in controlled trials, and given the likely relationship of higher plasma foscarnet levels to toxicity, it is recommended that most patients be started on maintenance treatment with a dose of 90 mg/kg/day. Escalation to 120 mg/kg/day may be considered should early reinduction be required because of retinitis progression. Some patients who show excellent tolerance to foscarnet sodium may benefit from initiation of maintenance treatment at 120 mg/kg/day earlier in their treatment.

An infusion pump must be used to control the rate of infusion with all doses. Adequate hydration is recommended to establish a diuresis, both prior to and during treatment to minimize renal toxicity, provided there are no clinical contraindications.

Patients who experience progression of retinitis while receiving foscarnet sodium maintenance therapy may be retreated with the induction and maintenance regimens given above or with a combination of foscarnet sodium injection and ganciclovir. **Because of physical incompatibility, foscarnet sodium and ganciclovir must NOT be mixed.**

Use in Patients with Abnormal Renal Function
Foscarnet sodium should be used with caution in patients with abnormal renal function because reduced plasma clearance of foscarnet will result in elevated plasma levels. In addition, foscarnet sodium has the potential to further impair renal function. Renal function must be monitored carefully at baseline and during induction and maintenance therapy with appropriate dose adjustments for foscarnet sodium. Foscarnet sodium is not recommended in patients undergoing hemodialysis because dosage guidelines have not been established.

Dose Adjustment
Foscarnet sodium dosing must be individualized according to the patient's renal function status. Refer to Table 13 of the Package Insert for recommended doses and adjust the dose as indicated. Even patients with serum creatinine in the normal range may require dose adjustment; therefore, the dose should be calculated at baseline and frequently thereafter.

OVERDOSAGE

There is no specific antidote for foscarnet sodium overdose. Hemodialysis and hydration may be of benefit in reducing drug plasma levels in patients who receive an overdosage of foscarnet sodium, but the effectiveness of these interventions has not been evaluated. The patient should be observed for signs and symptoms of renal impairment and electrolyte imbalance. Medical treatment should be instituted if clinically warranted.

INDICATIONS AND USAGE

CMV Retinitis
Foscarnet sodium injection is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). Combination therapy with foscarnet sodium and ganciclovir is indicated for patients who have relapsed after monotherapy with either drug. SAFETY AND EFFICACY OF FOSCARNET SODIUM HAVE NOT BEEN ESTABLISHED FOR TREATMENT OF OTHER CMV INFECTIONS (e.g., PNEUMONITIS, GASTROENTERITIS); CONGENITAL OR NEONATAL CMV DISEASE; OR NONIMMUNOCOMPROMISED INDIVIDUALS.

Mucocutaneous Acyclovir Resistant HSV Infections
Foscarnet sodium injection is indicated for the treatment of acyclovir-resistant mucocutaneous HSV infections in immunocompromised patients. SAFETY AND EFFICACY OF FOSCARNET SODIUM HAVE NOT BEEN ESTABLISHED FOR TREATMENT OF OTHER HSV INFECTIONS (e.g., RETINITIS, ENCEPHALITIS); CONGENITAL OR NEONATAL HSV DISEASE; OR HSV IN NONIMMUNOCOMPROMISED INDIVIDUALS.

HOW SUPPLIED/STORAGE AND HANDLING

Foscarnet sodium injection, 24 mg/mL for intravenous infusion, is supplied in 250 mL glass bottles containing 6000 mg foscarnet sodium (24 mg/mL) as follows:

NDC 0143-9192-01 250 mL bottles, cases of 10

Single-dose. Discard unused portion.

Store between 20° and 25°C (68° and 77°F) [See USP Controlled Room Temperature]. Protect from excessive heat (above 40°C) and from freezing. If refrigerated or exposed to temperatures below the freezing point, precipitation may occur. By keeping the bottle at room temperature with repeated shaking, the precipitate can be brought into solution again.

Foscarnet sodium injection should be used only if the bottle and seal are intact, a vacuum is present, and the solution is clear and colorless.

ENDING INFORMATION

Patient 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 FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

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Distributed by:
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922 USA

Document Identification Number: HK-2674-v1