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Press Release

Hikma launches Ganciclovir for Injection, USP

London, 22 June 2021 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Ganciclovir for Injection, USP, 500mg, in the US, through its US affiliate, Hikma Pharmaceuticals USA Inc.

Ganciclovir for Injection, USP is indicated for the treatment of cytomegalovirus (CMV) retinitis in immunocompromised adult patients, including patients with acquired immunodeficiency syndrome, and for the prevention of CMV disease in adult transplant recipients at risk for CMV disease.

According to IQVIA, US sales of Ganciclovir for Injection, USP, 500mg, were approximately $8 million in the 12 months ending April 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 Ganciclovir for Injection, USP, 500mg:

BOXED WARNING

WARNING: HEMATOLOGIC TOXICITY, IMPAIRMENT OF FERTILITY, FETAL TOXICITY, MUTAGENESIS AND CARCINOGENESIS

- **Hematologic Toxicity: Granulocytopenia, anemia, thrombocytopenia, and pancytopenia have been reported in patients treated with ganciclovir *[see Warnings and Precautions (5.1)].***
- **Impairment of Fertility: Based on animal data and limited human data, ganciclovir may cause temporary or permanent inhibition of spermatogenesis in males and suppression of fertility in females *[see Warnings and Precautions (5.3)]*.**
- **Fetal Toxicity: Based on animal data, ganciclovir has the potential to cause birth defects in humans *[see Warnings and Precautions (5.4)].***
- **Mutagenesis and Carcinogenesis: Based on animal data, ganciclovir has the potential to cause cancers in humans *[see Warnings and Precautions (5.5)].***

CONTRAINDICATIONS

Ganciclovir for injection is contraindicated in patients who have experienced a clinically significant hypersensitivity reaction (e.g., anaphylaxis) to ganciclovir, valganciclovir, or any component of the formulation.

WARNINGS & PRECAUTIONS

- **Hematologic Toxicity** – Granulocytopenia (neutropenia), anemia, thrombocytopenia and pancytopenia have been observed in patients treated with ganciclovir. The frequency and severity of these events vary widely in different patient populations. Ganciclovir should also be used with caution in patients with pre-existing cytopenias and in patients receiving myelosuppressive drugs or irradiation.
- **Renal Impairment** – Ganciclovir should be used with caution in patients with impaired renal function because the half-life and plasma/serum concentrations of ganciclovir will be increased due to reduced renal clearance. If renal function is impaired, dosage adjustments are recommended. Increased serum creatinine levels have been reported in elderly patients and in transplant recipients receiving concomitant nephrotoxic medications (i.e., cyclosporine and amphotericin B).
- **Impairment of Fertility** – Based on animal data and limited human data, ganciclovir at the recommended human dose (RHD) may cause temporary or permanent inhibition of spermatogenesis in males and may cause suppression of fertility in females. Advise patients that fertility may be impaired with the use of ganciclovir.
- **Fetal Toxicity** – Ganciclovir may cause fetal toxicity when administered to pregnant women based on findings in animal studies. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with ganciclovir. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir.
- **Mutagenesis and Carcinogenesis** – Animal data indicate that ganciclovir is mutagenic and carcinogenic. Ganciclovir should therefore be considered a potential carcinogen in humans.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

Hematologic Toxicity *[see Warnings and Precautions (5.1)]*

Renal Impairment *[see Warnings and Precautions (5.2)]*

Impairment of Fertility *[see Warnings and Precautions (5.3)]*

Fetal Toxicity *[see Warnings and Precautions (5.4)]*

Mutagenesis and Carcinogenesis *[see Warnings and Precautions (5.5)]*

Clinical Trial Experience in Adult Patients
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the

clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice. The most common adverse reactions and laboratory abnormalities reported in at least 20% of patients were pyrexia, diarrhea, leukopenia, nausea, anemia, asthenia, headache, cough, decreased appetite, dyspnea, abdominal pain, sepsis, hyperhidrosis, and blood creatinine increased.

Selected adverse reactions that occurred during clinical trials of ganciclovir for injection are summarized below, according to the participating study patient population.

Adverse Reactions in Patients with CMV Retinitis: Three controlled, randomized, phase 3 trials comparing ganciclovir for injection and ganciclovir capsules for maintenance treatment of CMV retinitis have been completed. During these trials, ganciclovir for injection or ganciclovir capsules were prematurely discontinued in 9% of subjects because of adverse reactions. Selected adverse reactions and laboratory abnormalities reported during the conduct of these controlled trials are summarized in Table 2 and Table 3 of the package insert.

Retinal Detachment: Retinal detachment has been observed in subjects with CMV retinitis both before and after initiation of therapy with ganciclovir for injection. Its relationship to therapy with ganciclovir for injection is unknown. Retinal detachment occurred in 11% of patients treated with ganciclovir for injection and in 8% of patients treated with ganciclovir capsules.

Adverse Reactions in Transplant Recipients: There have been three controlled clinical trials of ganciclovir for the prevention of CMV disease in transplant recipients. Selected laboratory abnormalities are summarized in Tables 4 and 5 of the package insert. Table 4 shows the frequency of neutropenia and thrombocytopenia and Table 5 shows the frequency of elevated serum creatinine values observed in these trials.

Other Adverse Reactions in Clinical Trials in Patients with CMV Retinitis and in Transplant Recipients
Adverse drug reactions with ganciclovir for injection or ganciclovir capsules in controlled clinical studies in either subjects with AIDS or transplant recipients are listed below. All these events occurred in at least 3 subjects.

Blood and lymphatic disorders: pancytopenia, bone marrow failure

Cardiac disorders: arrhythmia

Ear and labyrinth disorders: tinnitus, ear pain, deafness

Eye disorders: visual impairment, vitreous disorders, eye pain, conjunctivitis, macular edema

Gastrointestinal disorders: nausea, abdominal pain, dyspepsia, flatulence, constipation, mouth ulceration, dysphagia, abdominal distention, pancreatitis, gastrointestinal perforation, eructation, dry mouth

General disorders and administration site conditions: fatigue, injection site inflammation, edema, pain, malaise, asthenia, chest pain, multiple organ failure

Immune system disorders: hypersensitivity

Infections and infestations: candida infections including oral candidiasis, upper respiratory infection, influenza, urinary tract infection, cellulitis

Investigations: blood alkaline phosphatase increased, hepatic function abnormal, aspartate aminotransferase increased, alanine aminotransferase increased, creatinine clearance decreased

Metabolism and nutrition disorders: weight decreased

Musculoskeletal and connective tissue disorders: back pain, myalgia, arthralgia, muscle spasms, leg cramps, myasthenia

Nervous system disorders: headache, insomnia, dizziness, paresthesia, hypoaesthesia, seizure, somnolence, dysgeusia (taste disturbance), tremor

Psychiatric disorders: depression, confusional state, anxiety, agitation, psychotic disorder, thinking abnormal, abnormal dreams

Renal and urinary disorders: kidney failure, renal function abnormal, urinary frequency, hematuria

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Skin and subcutaneous tissues disorders: dermatitis, alopecia, dry skin, urticaria, rash

Vascular disorders: hypotension, hypertension, phlebitis, vasodilation

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of ganciclovir for injection or ganciclovir capsules. 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 disorders: hemolytic anemia, agranulocytosis, granulocytopenia

Cardiac disorders: cardiac arrest, conduction disorder, torsade de pointes, ventricular tachycardia

Congenital, familial and genetic disorders: congenital anomaly

Endocrine disorders: inappropriate antidiuretic hormone secretion

Eye disorders: cataracts, dry eyes

Gastrointestinal disorders: intestinal ulcer

Hepatobiliary disorders: cholelithiasis, cholestasis, hepatic failure, hepatitis

Immune system disorders: anaphylactic reaction, allergic reaction, vasculitis

Investigations: blood triglycerides increased

Metabolism and nutrition disorders: acidosis, hypercalcemia, hyponatremia

Musculoskeletal and connective tissue disorders: arthritis, rhabdomyolysis

Nervous system disorders: dysesthesia, dysphasia, extrapyramidal disorder, facial paralysis, amnesia, anosmia, myelopathy, cerebrovascular accident, third cranial nerve paralysis, aphasia, encephalopathy, intracranial hypertension

Psychiatric disorders: irritability, hallucinations

Renal and urinary disorders: renal tubular disorder, hemolytic uremic syndrome

Reproductive system and breast disorders: infertility, testicular hypotrophy

Respiratory, thoracic and mediastinal disorders: bronchospasm, pulmonary fibrosis

Skin and subcutaneous tissues disorders: exfoliative dermatitis, Stevens-Johnson syndrome

Vascular disorders: peripheral ischemia

DRUG INTERACTIONS

Drug-drug interaction studies were conducted in patients with normal renal function. Patients with impaired renal function may have increased concentrations of ganciclovir and the coadministered drug following concomitant administration of ganciclovir and drugs excreted by the same pathway as ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

Name of the Concomitant Drug	Change in the Concentration of Ganciclovir or Concomitant Drug	Clinical Comment
Imipenem-cilastatin	Unknown	Coadministration with imipenem- cilastatin is not recommended because generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin.
Cyclosporine or amphotericin B	Unknown	Monitor renal function when ganciclovir is coadministered with cyclosporine or amphotericin B because of potential increase in serum creatinine.
Mycophenolate mofetil (MMF)	↔ Ganciclovir (in patients with normal renal function) ↔ MMF (in patients with normal renal function)	Based on increased risk, patients should be monitored for hematological and renal toxicity.
Other drugs associated with myelosuppresion or nephrotoxicity (e.g., dapsone, doxorubicin, flucytosine, hydroxyurea, pentamidine, tacrolimus, trimethoprim/ sulfamethoxazole, vinblastine, vincristine and zidovudine)	Unknown	Because of potential for higher toxicity, coadministration with ganciclovir should be considered only if the potential benefits are judged to outweigh the risks.
Didanosine	↔ Ganciclovir ↑ Didanosine	Patients should be closely monitored for didanosine toxicity (e.g., pancreatitis).
Probenecid	↑ Ganciclovir	Ganciclovir dose may need to be reduced.

		Monitor for evidence of ganciclovir toxicity.

USE IN SPECIFIC POPULATIONS

Pregnancy
Although placental transfer of ganciclovir has been shown to occur based on *ex vivo* experiments with human placenta and in at least one case report in a pregnant woman, no adequate human data are available to establish whether ganciclovir poses a risk to pregnancy outcomes.

Most maternal CMV infections are asymptomatic or they may be associated with a self-limited mononucleosis-like syndrome. However, in immunocompromised patients (i.e., transplant patients or patients with AIDS), CMV infections may be symptomatic and may result in significant maternal morbidity and mortality. The transmission of CMV to the fetus is a result of maternal viremia and transplacental infection. Perinatal infection can also occur from exposure of the neonate to CMV shedding in the genital tract. Approximately 10% of children with congenital CMV infection are symptomatic at birth. Mortality in symptomatic infants is about 10% and approximately 50 to 90% of symptomatic surviving newborns experience significant morbidity, including mental retardation, sensorineural hearing loss, microcephaly, seizures, and other medical problems. The risk of congenital CMV infection resulting from primary maternal CMV infection may be higher and of greater severity than that resulting from maternal reactivation of CMV infection.

Lactation
No data are available regarding the presence of ganciclovir in human milk, the effects on the breastfed infant, or the effects on milk production. Advise nursing mothers that breastfeeding is not recommended during treatment with ganciclovir because of the potential for serious adverse reactions in nursing infants. Furthermore, the Centers for Disease Control and Prevention recommends that HIV-infected mothers not breastfeed their infants to avoid potential postnatal transmission of HIV.

Females and Males of Reproductive Potential
Females of reproductive potential should undergo pregnancy testing before initiation of treatment with ganciclovir. Because of the mutagenic and teratogenic potential of ganciclovir, females of reproductive potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with ganciclovir for injection. Because of its mutagenic potential, males should be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir. Ganciclovir at the recommended doses may cause temporary or permanent female and male infertility.

Pediatric Use
Safety and efficacy of ganciclovir for injection have not been established in pediatric patients.

Geriatric Use
Clinical studies of ganciclovir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Ganciclovir 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 renal clearance decreases with age, ganciclovir should be administered to elderly patients with special consideration of their renal status.

Renal Impairment
Dose reduction is recommended when administering ganciclovir to patients with renal impairment.

Hepatic Impairment
The safety and efficacy of ganciclovir have not been studied in patients with hepatic impairment.

DOSAGE AND ADMINISTRATION

Important Dosing and Administration Information
- To avoid phlebitis/pain at the infusion site, ganciclovir for injection must only be administered by intravenous infusion over 1 hour, preferably via plastic cannula, into a vein with adequate blood flow to permit rapid dilution and distribution.

- Do not administer ganciclovir for injection by rapid or bolus intravenous injection which may increase toxicity as a result of excessive plasma levels.
- The recommended dosage and infusion rate for ganciclovir should not be exceeded.
- Do not administer the reconstituted ganciclovir for injection solution intramuscularly or subcutaneously because it may result in severe tissue irritation due to high pH.
- Administration of ganciclovir for injection should be accompanied by adequate hydration.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Testing Before and During Treatment
- Females of reproductive potential should undergo pregnancy testing before initiation of treatment with ganciclovir.
- Complete blood counts with differential and platelet counts should be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in cytopenias, or in whom absolute neutrophil counts are less than 1000 cells/μL at the beginning of treatment.
- All patients should be monitored for renal function before and during treatment with ganciclovir and dose should be adjusted as needed.
- Patients with CMV retinitis should have frequent ophthalmological examinations during treatment with ganciclovir solution to monitor disease status and for other retinal abnormalities.

Recommended Dosage for Treatment of CMV Retinitis in Adult Patients with Normal Renal Function
Induction Dosage: The recommended initial dosage of ganciclovir for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 14 to 21 days.

Maintenance Dosage: Following induction treatment, the recommended maintenance dosage of ganciclovir is 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week.

Recommended Dosage for the Prevention of CMV Disease in Adult Transplant Recipients with Normal Renal Function
Induction Dosage: The recommended initial dosage of ganciclovir for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 7 to 14 days.

Maintenance Dosage: Following induction, the recommended maintenance dosage of ganciclovir is 5 mg/kg (given intravenously at a constant rate over 1 hour) once daily for 7 days per week, or 6 mg/kg once daily for 5 days per week until 100 to 120 days post-transplantation.

Recommended Dosage in Adult Patients with Renal Impairment
For patients with impairment of renal function, refer to Table 1 of the package insert for recommended doses of ganciclovir for induction and maintenance dosage for treatment of CMV retinitis and prevention of CMV disease in transplant recipients. Carefully monitor serum creatinine or creatinine clearance before and during treatment to allow for dosage adjustments in patients with impaired renal function.

Patients Undergoing Hemodialysis
Induction dosing for ganciclovir in patients undergoing hemodialysis should not exceed 1.25 mg/kg 3 times per week; and maintenance dosing should not exceed 0.625 mg/kg 3 times per week following each hemodialysis session. Ganciclovir should be given shortly after completion of the hemodialysis session, since hemodialysis has been shown to reduce plasma levels by approximately 50%.

Preparation of Ganciclovir for Injection
Ganciclovir for injection must be reconstituted and diluted under the supervision of a healthcare provider and administered as intravenous infusion. Each 10 mL clear glass vial contains 543 mg ganciclovir sodium equivalent to 500 mg of ganciclovir. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the vial and the table after reconstitution. The contents of the vial should be prepared for administration in the following manner:

1. Reconstitution Instructions:
   a) Reconstitute lyophilized ganciclovir for injection by injecting 10 mL of Sterile Water for Injection, USP, into the vial. Do not use bacteriostatic water for injection containing parabens. It is incompatible with

ganciclovir for injection and may cause precipitation.

b) Gently swirl the vial in order to ensure complete wetting of the product. Continue swirling until a clear reconstituted solution is obtained.
c) Visually inspect the reconstituted solution for particulate matter and discoloration prior to proceeding with infusion. Discard the vial if particulate matter or discoloration is observed.
d) Reconstituted solution in the vial is stable at room temperature (25° C (77°F)) for 12 hours. Do not refrigerate or freeze. Discard any unused portion of the reconstituted solution.

2. Infusion Instructions:
   a) Based on patient weight, the appropriate volume of the reconstituted solution (ganciclovir concentration 50 mg/mL) should be removed from the vial and added to an acceptable infusion fluid (typically 100 mL) for delivery over the course of 1 hour. Infusion concentrations greater than 10 mg/mL are not recommended. The following infusion fluids have been determined to be chemically and physically compatible with ganciclovir for injection solution: 0.9% Sodium Chloride, 5% Dextrose, Ringer's Injection and Lactated Ringer's Injection, USP.
   b) Ganciclovir for injection, when reconstituted with Sterile Water for Injection (non-bacteriostatic) and further diluted with 0.9% sodium chloride injection or other acceptable infusion fluid as specified above, should be used within 24 hours of dilution to reduce the risk of bacterial contamination. The diluted infusion solution should be refrigerated (2° to 8°C (36° to 46°F)). Do not freeze.

Handling and Disposal
Caution should be exercised in the handling and preparation of solutions of ganciclovir. Solutions of ganciclovir are alkaline (pH 11). Avoid direct contact of the skin or mucous membranes with ganciclovir solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. Wearing disposable gloves is recommended.

Because ganciclovir shares some of the properties of antitumor agents (i.e., carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs.

OVERDOSAGE
Reports of adverse reactions after overdoses with ganciclovir, some with fatal outcomes, have been received from clinical trials and during postmarketing experience. One or more of the following adverse reactions has been reported with overdoses:

Hematological toxicity: myelosuppression including pancytopenia, leukopenia, neutropenia, granulocytopenia, thrombocytopenia, bone marrow failure

Hepatotoxicity: hepatitis, liver function disorder

Renal toxicity: worsening of hematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine

Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting

Neurotoxicity: seizure

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of ganciclovir. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered in patients with cytopenias.

INDICATIONS AND USAGE

Treatment of CMV Retinitis
Ganciclovir for Injection, USP is indicated for the treatment of cytomegalovirus (CMV) retinitis in immunocompromised adult patients, including patients with acquired immunodeficiency syndrome (AIDS).

Prevention of CMV Disease in Transplant Recipients
Ganciclovir for Injection, USP is indicated for the prevention of CMV disease in adult transplant recipients at risk for CMV disease.

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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