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Press Release

Hikma launches Methotrexate Injection, USP and Methotrexate for Injection, USP

London, 3 May 2018 – Hikma Pharmaceuticals PLC (Hikma) (LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY), (rated Ba1 Moody's / BB+ S&P, both stable), announces that its wholly owned US subsidiary West-Ward Pharmaceuticals Corp. (West-Ward), has launched Methotrexate for Injection, USP in a 1g preservative-free presentation and Methotrexate Injection, USP 50mg/2mL, 2 mL vials.

According to IQVIA, US sales of Methotrexate for Injection, USP, 1g and Methotrexate Injection, USP, 50mg/2mL, were approximately $13 million in the 12 months ending March 2018.

Riad Mechlaoui, Chief Executive Officer Injectables, said, "We are pleased to launch Methotrexate for Injection, USP and Methotrexate Injection, USP, helping reduce the shortage of this product in the US market. Our continued progress in executing our injectables pipeline demonstrates our strong R&D, regulatory and manufacturing capabilities."

INDICATIONS

Methotrexate for Injection, USP and Methotrexate Injection, USP are indicated for use in the following:

- In the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.
- In acute lymphocytic leukemia, methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia.
- Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (cutaneous T cell lymphoma), and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas.
- Methotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor.
- Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation*. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.
- Methotrexate is indicated in the management of selected adults with severe, active rheumatoid arthritis (ACR criteria), or children with active polyarticular-course juvenile rheumatoid arthritis, who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

  Aspirin, (NSAIDs) and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

Important Safety Information about Methotrexate for Injection, USP and Methotrexate Injection, USP

WARNINGS:

- **FOR INTRATHECAL AND HIGH-DOSE THERAPY, USE THE PRESERVATIVE-FREE FORMULATION OF**

METHOTREXATE. DO NOT USE THE PRESERVED FORMULATION FOR INTRATHECAL OR HIGH-DOSE THERAPY BECAUSE IT CONTAINS BENZYL ALCOHOL.

- METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.
- DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.
- PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES.
- PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.
- THE USE OF METHOTREXATE HIGH-DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE. HIGH-DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.
- METHOTREXATE HAS BEEN REPORTED TO CAUSE FETAL DEATH AND/OR CONGENITAL ANOMALIES. THEREFORE, IT IS NOT RECOMMENDED FOR WOMEN OF CHILDBEARING POTENTIAL UNLESS THERE IS CLEAR MEDICAL EVIDENCE THAT THE BENEFITS CAN BE EXPECTED TO OUTWEIGH THE CONSIDERED RISKS. PREGNANT WOMEN WITH PSORIASIS OR RHEUMATOID ARTHRITIS SHOULD NOT RECEIVE METHOTREXATE.
- METHOTREXATE ELIMINATION IS REDUCED IN PATIENTS WITH IMPAIRED RENAL FUNCTION, ASCITES, OR PLEURAL EFFUSIONS. SUCH PATIENTS REQUIRE ESPECIALLY CAREFUL MONITORING FOR TOXICITY, AND REQUIRE DOSE REDUCTION OR, IN SOME CASES, DISCONTINUATION OF METHOTREXATE ADMINISTRATION.
- UNEXPECTEDLY SEVERE (SOMETIMES FATAL) BONE MARROW SUPPRESSION, APLASTIC ANEMIA, AND GASTROINTESTINAL TOXICITY HAVE BEEN REPORTED WITH CONCOMITANT ADMINISTRATION OF METHOTREXATE (USUALLY IN HIGH DOSAGE) ALONG WITH SOME NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS).
- METHOTREXATE CAUSES HEPATOTOXICITY, FIBROSIS AND CIRRHOSIS, BUT GENERALLY ONLY AFTER PROLONGED USE. ACUTELY, LIVER ENZYME ELEVATIONS ARE FREQUENTLY SEEN. THESE ARE USUALLY TRANSIENT AND ASYMPTOMATIC, AND ALSO DO NOT APPEAR PREDICTIVE OF SUBSEQUENT HEPATIC DISEASE. LIVER BIOPSY AFTER SUSTAINED USE OFTEN SHOWS HISTOLOGIC CHANGES, AND FIBROSIS AND CIRRHOSIS HAVE BEEN REPORTED; THESE LATTER LESIONS MAY NOT BE PRECEDED BY SYMPTOMS OR ABNORMAL LIVER FUNCTION TESTS IN THE PSORIASIS POPULATION. FOR THIS REASON, PERIODIC LIVER BIOPSIES ARE USUALLY RECOMMENDED FOR PSORIATIC PATIENTS WHO ARE UNDER LONG-TERM TREATMENT. PERSISTENT ABNORMALITIES IN LIVER FUNCTION TESTS MAY PRECEDE APPEARANCE OF FIBROSIS OR CIRRHOSIS IN THE RHEUMATOID ARTHRITIS POPULATION.
- METHOTREXATE-INDUCED LUNG DISEASE, INCLUDING ACUTE OR CHRONIC INTERSTITIAL PNEUMONITIS, IS A POTENTIALLY DANGEROUS LESION, WHICH MAY OCCUR ACUTELY AT ANY TIME DURING THERAPY AND HAS BEEN REPORTED AT LOW DOSES. IT IS NOT ALWAYS FULLY REVERSIBLE AND FATALITIES HAVE BEEN REPORTED. PULMONARY SYMPTOMS (ESPECIALLY A DRY, NONPRODUCTIVE COUGH) MAY REQUIRE INTERRUPTION OF TREATMENT AND CAREFUL INVESTIGATION.
- DIARRHEA AND ULCERATIVE STOMATITIS REQUIRE INTERRUPTION OF THERAPY; OTHERWISE, HEMORRHAGIC ENTERITIS AND DEATH FROM INTESTINAL PERFORATION MAY OCCUR.
- MALIGNANT LYMPHOMAS, WHICH MAY REGRESS FOLLOWING WITHDRAWAL OF METHOTREXATE, MAY OCCUR IN PATIENTS RECEIVING LOW-DOSE METHOTREXATE AND, THUS, MAY NOT REQUIRE CYTOTOXIC TREATMENT. DISCONTINUE METHOTREXATE FIRST AND, IF THE LYMPHOMA DOES NOT REGRESS, APPROPRIATE TREATMENT SHOULD BE INSTITUTED.
- LIKE OTHER CYTOTOXIC DRUGS, METHOTREXATE MAY INDUCE "TUMOR LYSIS SYNDROME" IN PATIENTS WITH RAPIDLY GROWING TUMORS. APPROPRIATE SUPPORTIVE AND PHARMACOLOGIC MEASURES MAY PREVENT OR ALLEVIATE THIS COMPLICATION.
- SEVERE, OCCASIONALLY FATAL, SKIN REACTIONS HAVE BEEN REPORTED FOLLOWING SINGLE OR MULTIPLE DOSES OF METHOTREXATE. REACTIONS HAVE OCCURRED WITHIN DAYS OF ORAL, INTRAMUSCULAR, INTRAVENOUS, OR INTRATHECAL METHOTREXATE ADMINISTRATION. RECOVERY

HAS BEEN REPORTED WITH DISCONTINUATION OF THERAPY.

- POTENTIALLY FATAL OPPORTUNISTIC INFECTIONS, ESPECIALLY PNEUMOCYSTIS CARINII PNEUMONIA, MAY OCCUR WITH METHOTREXATE THERAPY.
- METHOTREXATE GIVEN CONCOMITANTLY WITH RADIOTHERAPY MAY INCREASE THE RISK OF SOFT TISSUE NECROSIS AND OSTEONECROSIS.

CONTRAINDICATIONS

- Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate injection is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of 3 months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.
- Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.
- Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.
- Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.
- Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia, should not receive methotrexate.
- Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS

- **For intrathecal and high-dose methotrexate therapy, use the preservative-free formulation of methotrexate. Do not use the preserved formulation of methotrexate for intrathecal or high dose therapy because it contains benzyl alcohol.**
- Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.

PRECAUTIONS

General

- Procedures for proper handling and disposal of anticancer drugs should be considered.
- Methotrexate has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses.
- The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.
- Some adverse effects, such as dizziness and fatigue, may affect the ability to drive or operate machinery.

Information for Patients

- Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

- Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity.
- Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.
- Methotrexate causes embryotoxicity, abortion, and fetal defects. It has also been reported to cause impairment of fertility.
- Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly.
- Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation.

DRUG INTERACTIONS

- Non-steroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.
- Caution should be taken when NSAIDS or salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.
- Displacement of drugs such as; salicylates, phenylbutazone, phenytoin, and sulfonamides may increase toxicity. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.
- Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.
- Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.
- Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.
- Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate.
- Folate deficiency states may increase methotrexate toxicity.

ADVERSE EVENTS

- The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, fatigue, chills and fever, dizziness, and decreased resistance to infection.
- Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

OVERDOSAGE

- Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible.
- In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules.
- Accidental intrathecal overdosage may require intensive systemic support, high-dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion.
- Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were

reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy have also been reported.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. Information for patients should be shared with the patient prior to administration.

For complete product information, please refer to the Package Insert for Methotrexate for Injection, USP and Methotrexate Injection, USP for full prescribing information, also available on **www.west-ward.com**.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

Manufactured by:
THYMOORGAN PHARMAZIE GmbH,
Schiffgraben 23, 38690 Goslar, Germany

Distributed by:
West-Ward Pharmaceuticals Corp.
Eatontown, NJ 07724 USA

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Enquiries

Hikma Pharmaceuticals PLC

Susan Ringdal, VP Corporate Strategy and Investor Relations	+44 (0)20 7399 2760/ +44 7776 477050
Virginia Spring, Investor Relations Manager	+44 (0)20 3892 4389/ +44 7973 679502

FTI Consulting

Ben Atwell/Brett Pollard	+44 (0)20 3727 1000

About Hikma

Hikma helps puts better health within reach every day for millions of people in more than 50 countries around the world. For 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. We're 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 8,500 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner in the MENA region, 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.