hikma.

Press Release

Hikma Launches Epirubicin Hydrochloride Injection, USP

London, 5 April 2018 – Hikma Pharmaceuticals PLC (Hikma, Group) (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 Epirubicin Hydrocholoride Injection, USP, 50mg/25mL and 200mg/100mL vials, the generic equivalent to Ellence®.[1]

West-Ward's Epirubicin Hydrochloride Injection, USP is indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.

According to IQVIA, US sales of Epirubicin Hydrochloride Injection, USP, 50mg/25mL and 200mg/100mL vials, were approximately $0.8 million in the 12 months ending January 2018.

Important Safety Information About Epirubicin Hydrochloride Injection, USP

WARNING: RISK OF TISSUE NECROSIS, CARDIAC TOXICITY, SECONDARY ACUTE MYELOGENOUS LEUKEMIA, AND MYELOSUPPRESSION

- SEVERE LOCAL TISSUE NECROSIS WILL OCCUR IF THERE IS EXTRAVASATION DURING ADMINISTRATION. EPIRUBICIN HYDROCHLORIDE MUST NOT BE GIVEN BY THE INTRAMUSCULAR OR SUBCUTANEOUS ROUTE.
- CARDIAC TOXICITY, INCLUDING FATAL CONGESTIVE HEART FAILURE (CHF), MAY OCCUR EITHER DURING THERAPY WITH EPIRUBICIN HYDROCHLORIDE OR MONTHS TO YEARS AFTER TERMINATION OF THERAPY. THE PROBABILITY OF DEVELOPING CLINICALLY EVIDENT CHF IS ESTIMATED AS APPROXIMATELY 0.9% AT A CUMULATIVE DOSE OF 550 MG/M^2, 1.6% AT 700 MG/M^2, AND 3.3% AT 900 MG/M^2. IN THE ADJUVANT TREATMENT OF BREAST CANCER, THE MAXIMUM CUMULATIVE DOSE USED IN CLINICAL TRIALS WAS 720 MG/M^2. THE RISK OF DEVELOPING CHF INCREASES RAPIDLY WITH INCREASING TOTAL CUMULATIVE DOSES OF EPIRUBICIN HYDROCHLORIDE IN EXCESS OF 900 MG/M^2; THIS CUMULATIVE DOSE SHOULD ONLY BE EXCEEDED WITH EXTREME CAUTION. ACTIVE OR DORMANT CARDIOVASCULAR DISEASE, PRIOR OR CONCOMITANT RADIOTHERAPY TO THE MEDIASTINAL/PERICARDIAL AREA, PREVIOUS THERAPY WITH OTHER ANTHRACYCLINES OR ANTHRACENEDIONES, OR CONCOMITANT USE OF OTHER CARDIOTOXIC DRUGS MAY INCREASE THE RISK OF CARDIAC TOXICITY. CARDIAC TOXICITY WITH EPIRUBICIN HYDROCHLORIDE MAY OCCUR AT LOWER CUMULATIVE DOSES WHETHER OR NOT CARDIAC RISK FACTORS ARE PRESENT.
- SECONDARY ACUTE MYELOGENOUS LEUKEMIA (AML) HAS BEEN REPORTED IN PATIENTS WITH BREAST CANCER TREATED WITH ANTHRACYCLINES, INCLUDING EPIRUBICIN. THE OCCURRENCE OF REFRACTORY SECONDARY LEUKEMIA IS MORE COMMON WHEN SUCH DRUGS ARE GIVEN IN COMBINATION WITH DNA-DAMAGING ANTINEOPLASTIC AGENTS, WHEN PATIENTS HAVE BEEN HEAVILY PRETREATED WITH CYTOTOXIC DRUGS, OR WHEN DOSES OF ANTHRACYCLINES HAVE BEEN ESCALATED. THE CUMULATIVE RISK OF DEVELOPING TREATMENT-RELATED AML OR MYELODYSPLASTIC SYNDROME (MDS), IN 7110 PATIENTS WITH BREAST CANCER WHO RECEIVED ADJUVANT TREATMENT WITH EPIRUBICIN HYDROCHLORIDE-CONTAINING REGIMENS, WAS ESTIMATED AS 0.27% AT 3 YEARS, 0.46% AT 5 YEARS, AND 0.55% AT 8 YEARS.
- SEVERE MYELOSUPPRESSION MAY OCCUR.

[1] Ellence® is a registered trademark of Pfizer, Inc.

Patients should not be treated with Epirubicin Hydrochloride Injection if they have any of the following conditions: baseline neutrophil count < 1500 cells/mm3; cardiomyopathy and/or heart failure, recent myocardial infarction, severe arrhythmias; previous treatment with anthracyclines up to the maximum cumulative dose; hypersensitivity to epirubicin, other anthracyclines, or anthracenediones; or severe hepatic dysfunction.

The following warnings and precautions should be taken when administering Epirubicin Hydrochloride Injection, USP:

- Administer epirubicin hydrochloride only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Protective measures should be taken in the preparation and administration of epirubicin.
- Prior to treatment with epirubicin hydrochloride complete a baseline assessment of blood counts; serum levels of total bilirubin, AST, and creatinine; and cardiac function as measured by left ventricular ejection function (LVEF). Myelosuppression is usually the dose-limiting toxicity. Monitor patients during therapy for possible clinical complications due to myelosuppression.
- May suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anemia.
- Evaluate serum total bilirubin and AST levels before and during treatment with epirubicin hydrochloride. Patients with elevated bilirubin and AST levels may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients. Do not use epirubicin hydrochloride in patients with severe hepatic impairment.
- Assess serum creatinine before and during therapy. Dosage adjustment is necessary in patients with serum creatinine > 5 mg/dL. Patients undergoing dialysis have not been studied.
- Epirubicin hydrochloride may induce hyperuricemia and other metabolic abnormalities may occur.
- Immunosuppression: Avoid vaccination with a live or live-attenuated vaccine in patients receiving epirubicin hydrochloride as this may result in serious or fatal infections.
- Venous sclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Extravasation of epirubicin hydrochloride during the infusion may cause local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis. Facial flushing, as well as local erythematous streaking along the vein, may be indicative of excessively rapid administration. It may precede local phlebitis or thrombophlebitis. Patients administered the 120 mg/m^2 regimen of epirubicin hydrochloride as a component of combination chemotherapy should also receive prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole or a fluoroquinolone.
- May cause nausea and vomiting. Consider prophylactic use of antiemetics before administration of epirubicin hydrochloride, particularly when given in conjunction with other drugs that may cause nausea and vomiting.
- Administration of epirubicin hydrochloride after previous radiation therapy may induce an inflammatory recall reaction at the site of the irradiation.
- Thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of epirubicin hydrochloride.
- Discontinue cimetidine treatment during epirubicin treatment.
- Epirubicin can cause fetal harm, consult patient of the potential hazard to a fetus. Advise women of child-bearing potential to avoid becoming pregnant during treatment.
- May damage testicular tissue and spermatozoa. Possible spear DNA damage raises concern about genetic abnormalities in fetuses. The duration of this effect is uncertain. Advise males of the possible effect.
- Assess blood counts, including absolute neutrophil counts, and liver function before and during each cycle of therapy with epirubicin hydrochloride. Perform repeated evaluations of LVEF during therapy.

In early breast cancer, acute adverse events occurring in ≥10% of patients are leukopenia, neutropenia, anemia, thrombocytopenia, amenhorrhea, lethargy, nausea/vomiting, mucositis, diarrhea, infection, conjunctivitis/keratitis, alopecia, local toxicity and rash/itch.

Acute and delayed toxicities include reversible leukopenia, neutropenia or severe myelosuppression. Nausea, vomiting, occasional diarrhea and abdominal pain can also occur. Urticaria and anaphylaxis have been reported in patients treated with epirubicin hydrochloride. The risk of developing secondary leukemia is increased with cumulative doses of epirubicin.

The following adverse reactions have been reported in the post-approval use of epirubicin hydrochloride injection: Sepsis, pneumonia, anaphylaxis, metabolism and nutrition disorders (i.e., dehydration and hyperuricemia), vascular disorders (i.e., shock, haemorrhage, embolism arterial, thrombophlebitis, phlebitis), pulmonary embolism,

gastrointestinal disorders (i.e., erosions, ulcerations, pain or burning sensation, bleeding, hyperpigmentation of the oral mucosa), skin and subcutaneous tissue disorders (erythema, flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction), urticarial), red coloration of urine, fever, chills and chemical cystitis (following intravesical administration).

Do not administer epirubicin in combination with other cardiotoxic agents unless the patient's cardiac function closely monitored. Concomitant use of epirubicin hydrochloride with other cardioactive compounds that could cause heart failure (e.g., calcium channel blockers), requires close monitoring of cardiac function throughout treatment. Discontinue use of cimetidine during treatment with epirubicin. Epirubicin hydrochloride used in combination with other cytotoxic drugs may show on-treatment additive toxicity, especially hematologic and gastrointestinal effects. Epirubicin is extensively metabolized by the liver, changes in hepatic function may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy, and/or toxicity.

Nursing mothers: Discontinue nursing prior to taking epirubicin hydrochloride.

Pediatric Use: Safety and effectiveness of epirubucin hydrochloride in pediatric patients have not been established. Pediatric patients may be at greater risk for anthracycline-induced acute manifestations of cardiotoxicity and for chronic CHF.

Geriatric Use: Care should be taken in monitoring toxicity when epirubicin hydrochloride is administered to female patients ≥ 70 years of age.

There is no known antidote for overdoses of epirubicin hydrochloride. If an overdose occurs, provide supportive treatment (including antibiotic therapy, blood and platelet transfusions, colony-stimulating factors, and intensive care as needed) until the recovery of toxicities. Delayed CHF has been observed months after anthracycline administration. Observe patients carefully over time for signs of CHF and provide with appropriate supportive therapy.

Patient Counseling Information should be shared with the patient prior to administration.

Please refer to the Package Insert for full prescribing information, available here. Additional information on West-Ward Pharmaceuticals Corp. products is available at http://www.west-ward.com.

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

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

-- ENDS --

Enquiries

Hikma Pharmaceuticals PLC

Susan Ringdal — +44 (0)20 7399 2760/ +44 7776 477050

VP Corporate Strategy and Investor Relations

Virginia Spring — +44 (0)20 3892 4389/ +44 7973 679502

Investor Relations Manager

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.