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Press Release

Hikma launches Bleomycin for Injection, USP

London, 18 July 2018 – Hikma Pharmaceuticals PLC (Hikma, Group) (LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated Ba1 Moody's / BB+ S&P, both stable) announces that Hikma Pharmaceuticals USA Inc., formerly known as West-Ward Pharmaceuticals, has launched Bleomycin for Injection, USP, 15U and 30U, the generic equivalent to Blenoxane®.[1]

Hikma's Bleomycin for Injection, USP should be considered a palliative treatment. It has been shown to be useful in the management of certain types of Squamous Cell Carcinoma, Lymphomas, Testicular Carcinoma, and Malignant Pleural Effusion.

According to IQVIA, US sales of Bleomycin for Injection, USP, 15U and 30U, were approximately $4 million in the 12 months ending May 2018.

Important Safety Information about Bleomycin for Injection, USP

- IT IS RECOMMENDED THAT BLEOMYCIN BE ADMINISTERED UNDER THE SUPERVISION OF A QUALIFIED PHYSICIAN EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPEUTIC AGENTS. APPROPRIATE MANAGEMENT OF THERAPY AND COMPLICATIONS IS POSSIBLE ONLY WHEN ADEQUATE DIAGNOSTIC AND TREATMENT FACILITIES ARE READILY AVAILABLE.

  PULMONARY FIBROSIS IS THE MOST SEVERE TOXICITY ASSOCIATED WITH BLEOMYCIN. THE MOST FREQUENT PRESENTATION IS PNEUMONITIS OCCASIONALLY PROGRESSING TO PULMONARY FIBROSIS. ITS OCCURRENCE IS HIGHER IN ELDERLY PATIENTS AND IN THOSE RECEIVING GREATER THAN 400 UNITS TOTAL DOSE, BUT PULMONARY TOXICITY HAS BEEN OBSERVED IN YOUNG PATIENTS AND THOSE TREATED WITH LOW DOSES.

  A SEVERE IDIOSYNCRATIC REACTION CONSISTING OF HYPOTENSION, MENTAL CONFUSION, FEVER, CHILLS, AND WHEEZING HAS BEEN REPORTED IN APPROXIMATELY 1% OF LYMPHOMA PATIENTS TREATED WITH BLEOMYCIN.

- Bleomycin is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.
- The following warnings and precautions should be taken when administering Bleomycin for Injection, USP:
  - Patients receiving bleomycin must be observed carefully and frequently during and after therapy.
  - Use with extreme caution in patients with significant impairment of renal function or compromised pulmonary function.
  - Pulmonary toxicities occur in 10% of treated patients. In approximately 1%, the nonspecific pneumonitis induced by bleomycin progresses to pulmonary fibrosis and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended.
  - A severe idiosyncratic reaction (similar to anaphylaxis) consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin.

[1] Blenoxane® is a registered trademark of Bristol-Myers Squibb Company Corporation

Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses.

- Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported. These toxicities may occur at any time after initiation of therapy.

- Bleomycin can cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in rats. There have been no studies in pregnant women.

- If bleomycin is used during pregnancy, or if the patient becomes pregnant during treatment, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with bleomycin.

- Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued by women receiving bleomycin therapy.

- Patients with creatinine clearance values of less than 50 mL/min should be treated with caution and their renal function should be carefully monitored during administration.

- The carcinogenic potential of bleomycin in humans is unknown. A study in male rats demonstrated an increased incidence of nodular hyperplasia after induced lung carcinogenesis by nitrosamines, followed by treatment with bleomycin. In another study where the drug was administered to rats by subcutaneous injection at about 30% of the recommended human dose, necropsy findings included dose related injection site fibrosarcomas as well as various renal tumors.

- Bleomycin has been shown to be mutagenic both *in vitro* and *in vivo*.

- The effects of bleomycin on fertility have not been studied.

- Safety and effectiveness of bleomycin in pediatric patients have not been established.

- In clinical trials, pulmonary toxicity was more common in patients older than 70 years than in younger patients. Other reported clinical experience has not identified other differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

- Bleomycin 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 it may be useful to monitor renal function

- Caution should be exercised when handling bleomycin for injection. Procedures for proper handling and disposal of anticancer drugs should be utilized.

- The most serious side effects are pulmonary adverse reactions, occurring in approximately 10% of treated patients. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Approximately 1% of patients treated have died of pulmonary fibrosis. Pulmonary toxicity is both dose and age related, being more common in patients over 70 years of age and in those receiving over 400 units total dose. This toxicity, however, is unpredictable and has been seen in young patients receiving low doses. Some reports have suggested that the risk of pulmonary toxicity may be increased when bleomycin is used in combination with G-CSF (filgrastim) or other cytokines.

- Because of bleomycin's sensitization of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered in surgery. While long exposure to very high oxygen concentrations is a known cause of lung damage, after bleomycin administration, lung damage can occur at lower concentrations that are usually considered safe.

- Sudden onset of an acute chest pain syndrome suggestive of pleuropericarditis has been reported during bleomycin infusions. Although each patient must be individually evaluated, further courses of bleomycin do not appear to be contraindicated.

- Pulmonary adverse events which may be related to the intrapleural administration of bleomycin have been reported.

- Idiosyncratic reactions, similar to anaphylaxis, has been reported in approximately 1% of lymphoma patients. The reaction may be immediate or delayed for several hours, and usually occurs after the first or second dose. It consists of hypotension, mental confusion, fever, chills, and wheezing.

- Integument and mucous membrane adverse reactions have been reported in approximately 50% of treated patients. These consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperkeratosis, nail changes, alopecia, pruritus, and stomatitis have also been reported. It was necessary to discontinue bleomycin therapy in 2% of treated patients because of these toxicities. Scleroderma-like skin changes have been reported.

- Intrapleural administration of bleomycin has been associated with local pain. Death has been reported in association with bleomycin pleurodesis in seriously ill patients.

- Vascular toxicities coincident with the use of bleomycin in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS) or cerebral arteritis.

- Fever, chills, malaise, and vomiting have been reported. Anorexia and weight loss have been reported and may persist long after termination of treatment. Pain at tumor site, phlebitis, and other local reactions have been reported.

- Because bleomycin is eliminated predominantly through renal extraction, the administration of nephrotoxic drugs with bleomycin may affect its renal clearance. Fatal bleomycin pulmonary toxicity has been reported in a patient with unrecognized cisplatin-induced oliguric renal failure.

INDICATIONS AND USAGE

Bleomycin for Injection, USP should be considered a palliative treatment. It has been shown to be useful in the management of the following:

Squamous Cell Carcinoma

Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingivae, epiglottis, skin, larynx), penis, cervix, and vulva. The response to bleomycin is poorer in patients with previously irradiated head and neck cancer.

Lymphomas

Hodgkin's disease, non-Hodgkin's lymphoma.

Testicular Carcinoma

Embryonal cell, choriocarcinoma, and teratocarcinoma.

Bleomycin for Injection, USP has also been shown to be useful in the management of:

Malignant Pleural Effusion

Bleomycin is effective as a sclerosing agent for the treatment of malignant pleural effusion and prevention of recurrent pleural effusions.

Please refer to the Package Insert for full prescribing information. Additional information on Hikma US products is available on www.hikma.com/us.

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THYMOORGAN PHARMAZIE GmbH,
Schiffgraben 23, 38690 Goslar, Germany

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Eatontown, NJ 077224 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 put 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.