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Press Release

Hikma launches Azacitidine for Injection

London, 10 September, 2020 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Azacitidine for Injection, 100mg, the generic version of Vidaza®[1] in the United States through its US affiliate, Hikma Pharmaceuticals USA Inc.

According to IQVIA, US sales of Azacitidine for Injection, 100mg, were approximately $82 million in the 12 months ending July 2020.

Azacitidine for Injection is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).

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 -

Enquiries

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated Ba1/stable Moody's and BBB-/stable S&P)

Hikma helps put better health within reach every day for millions of people in more than 50 countries 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-

[1] Vidaza® is a registered trademark of Celegene Inc.

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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

Important Safety Information for Azacitidine for Injection, 100mg:

CONTRAINDICATIONS

Advanced Malignant Hepatic Tumors
Azacitidine for Injection is contraindicated in patients with advanced malignant hepatic tumors.

Hypersensitivity to Azacitidine or Mannitol
Azacitidine for Injection is contraindicated in patients with a known hypersensitivity to azacytidine or mannitol.

WARNINGS & PRECAUTIONS

- Azacitidine for Injection causes anemia, neutropenia and thrombocytopenia. Monitor complete blood counts frequently for response and/or toxicity, at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response.
- Because azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L.
- Azacitidine is contraindicated in patients with advanced malignant hepatic tumors. Monitor liver chemistries prior to initiation of therapy and with each cycle.
- Safety and effectiveness of Azacitidine for Injection in patients with MDS and hepatic impairment have not been studied as these patients were excluded from the clinical trials.
- Renal toxicity ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents for non-MDS conditions.
- Renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with azacitidine and etoposide. Monitor serum creatinine and electrolytes prior to initiation of therapy and with each cycle. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of BUN or serum creatinine occur, reduce or hold the dose.
- Patients with renal impairment may be at increased risk for renal toxicity. Also, azacitidine and its metabolites are primarily excreted by the kidney. Therefore, monitor these patients closely for toxicity. Patients with MDS and renal impairment were excluded from the clinical studies.
- Azacitidine for Injection may cause fatal or serious tumor lysis syndrome, including in patients with MDS. Tumor lysis syndrome may occur despite concomitant use of allopurinol. Assess baseline risk and monitor and treat as appropriate.
- Based on the mechanism of action and findings in animals, Azacitidine for Injection can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant rats via a single intraperitoneal (IP) dose approximating 8% of the recommended human daily dose caused fetal death and anomalies.
- Advise females with reproductive potential to avoid pregnancy during treatment with Azacitidine for Injection. Men should be advised to not father a child while receiving treatment with Azacitidine for Injection.

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ADVERSE REACTIONS

The following adverse reactions are described in other labeling sections:

- Anemia, Neutropenia and Thrombocytopenia
- Hepatotoxocity in Patients with Severe Pre-existing Hepatic Impairment
- Renal Toxicity
- Tumor Lysis Syndrome
- Embryo-Fetal Risk

Most Commonly Occurring Adverse Reactions (Subcutaneous or Intravenous Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, ecchymosis. The most common adverse reactions by intravenous route also included petechiae, rigors, weakness and hypokalemia.

Adverse Reactions Most Frequently (>2%) Resulting in Clinical Intervention (Subcutaneous or Intravenous Route):
Discontinuation: leukopenia, thrombocytopenia, neutropenia.
Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.
Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

Refer to package insert for Adverse Reactions in Clinical Trials: the adverse reactions are broken down into most frequently observed (≥ 5.0% in treated patients) and less frequently observed (< 5% in treated patients).

The following adverse reactions have been identified during postmarketing use of Azacitidine for Injection. 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.

- Interstitial lung disease
- Tumor lysis syndrome
- Injection site necrosis
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Necrotizing fasciitis (including fatal cases)
- Differentiation syndrome

DRUG INTERACTIONS

No formal clinical drug interaction studies with azacitidine have been conducted.

An *in vitro* study of azacitidine incubation in human liver fractions indicated that azacitidine may be metabolized by the liver. Whether azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied.

An *in vitro* study with cultured human hepatocytes indicated that azacitidine at concentrations up to 100 µM (IV C_{max} = 10.6 µM) does not cause any inhibition of CYP2B6 and CYP2C8. The potential of azacitidine to inhibit other cytochrome P450 (CYP) enzymes is not known.

In vitro studies with human cultured hepatocytes indicate that azacitidine at concentrations of 1.0 µM to 100 µM does not induce CYP 1A2, 2C19, or 3A4/5.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Based on its mechanism of action and findings in animals, Azacitidine for Injection can cause fetal harm when administered to a pregnant woman. There are no data on the use of azacitidine in pregnant women. Azacitidine was teratogenic and caused embryo-fetal lethality in animals at doses lower than the recommended human daily dose. Advise pregnant women of the potential risk to the fetus.

Lactation
Risk Summary
There is no information regarding the presence of azacitidine in human milk, the effects of Azacitidine for Injection on the breastfed infant, or the effects of Azacitidine for Injection on milk production. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for azacitidine in animal studies and the potential for serious adverse reactions in nursing infants from Azacitidine for Injection, advise patients not to breastfeed during treatment with Azacitidine for Injection.

Females and Males of Reproductive Potential
Based on its mechanism of action and findings in animals, Azacitidine for Injection can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating Azacitidine for Injection. Advise females of reproductive potential to avoid pregnancy during treatment with Azacitidine for Injection. Males with female sexual partners of reproductive potential should not father a child and should use effective contraception during treatment with Azacitidine for Injection. Based on animal data, azacitidine could have an effect on male or female fertility.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Of the total number of patients in Studies 1, 2 and 3, 62% were 65 years and older and 21% were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. In addition, there were no relevant differences in the frequency of adverse reactions observed in patients 65 years and older compared to younger patients.

Of the 179 patients randomized to azacitidine in Study 4, 68% were 65 years and older and 21% were 75 years and older. Survival data for patients 65 years and older were consistent with overall survival results. The majority of adverse reactions occurred at similar frequencies in patients < 65 years of age and patients 65 years of age and older.

Elderly patients are more likely to have decreased renal function. Monitor renal function in these patients.

DOSAGE AND ADMINISTRATION

Refer to package insert for dosage and administration instructions specific to the First Treatment Cycle, Subsequent Treatment Cycles, Dosage Adjustment Based on Hematology Laboratory Values, Dosage Adjustment Based on Serum Electrolytes and Renal Toxicity, and Use in Geriatric Patients.

Preparation of Azacitidine for Injection
Azacitidine for Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.

The Azacitidine for Injection vial is single-dose and does not contain any preservatives. Discard unused portions of each vial properly. Do not save any unused portions for later administration.

Instructions for Subcutaneous Administration

Refer to package insert for dosage and administration instructions specific to Subcutaneous Administration: Reconstitution, Preparation for Immediate Subcutaneous Administration, Preparation for Delayed Subcutaneous Administration, Subcutaneous Administration, and Suspension Stability.

Instructions for Intravenous Administration
Refer to package insert for dosage and administration instructions specific to Intravenous Administration: Reconstitution, Intravenous Solution Incompatibility, Intravenous Administration, and Solution Stability.

Handling and Disposal
Azacitidine for Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.

OVERDOSAGE

One case of overdose with Azacitidine for Injection was reported during clinical trials. A patient experienced diarrhea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m^2, almost 4 times the recommended starting dose. The events resolved without sequelae, and the correct dose was resumed the following day. In the event of overdosage, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for Azacitidine for Injection overdosage.

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.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit http://www.fda.gov/medwatch or call 1-800-FDA-1088.

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