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Press Release

Hikma launches Imatinib Mesylate Tablets

London, 29 October 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 Corp., has launched Imatinib mesylate Tablets, 100mg and 400mg, the generic equivalent to Gleevec®.[1]

Hikma's Imatinib Mesylate (100 mg and 400 mg tablets) is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- Patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in the chronic phase (CP) after failure of interferon-alpha therapy.
- Adult patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements as determined with an FDA-approved test.
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation as determined with an FDA-approved test or with c-Kit mutational status unknown.
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.
- Adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP).

According to IQVIA, US sales of Imatinib Mesylate Tablets were approximately $831 million in the 12 months ending August 2018.

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[1] Gleevec® is a registered trademark of Novartis

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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.

Important Safety Information for Imatinib Mesylate Tablets 100mg and 400mg:

IMPORTANT SAFETY INFORMATION

- Imatinib mesylate is often associated with edema and occasionally serious fluid retention. Weigh and monitor patients regularly for signs and symptoms of fluid retention. Investigate unexpected rapid weight gain carefully and provide appropriate treatment. In the CML studies, the probability of edema tended to increase among older patients (>65 years) or those taking higher doses of imatinib mesylate. Severe superficial edema was reported in 1.5% of newly diagnosed CML patients taking imatinib mesylate, and in 2%–6% of other adult CML patients taking imatinib mesylate. In addition, other severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) reactions were reported in 1.3% of newly diagnosed CML patients taking imatinib mesylate, and in 2%–6% of other adult CML patients taking imatinib mesylate. Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuretics. In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing imatinib mesylate and nilotinib, severe (Grade 3 or 4) fluid retention occurred in 2.5% of patients receiving imatinib

mesylate and in 3.9% of patients receiving nilotinib 300 mg twice daily. Effusions (including pleural effusion, pericardial effusion, ascites) or pulmonary edema were observed in 2.1% (none were Grade 3 or 4) of patients in the imatinib mesylate arm and 2.2% (0.7% Grade 3 or 4) of patients in the nilotinib 300 mg twice daily arm.

- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have been reported. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (eg, every 2–3 months). In CML, the occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. In pediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anemia. These generally occur within the first several months of therapy. Dose reduction, treatment interruption, or in rare cases discontinuation of treatment may be required for severe neutropenia or thrombocytopenia (see full Prescribing Information for dose adjustment recommendations).

- Congestive heart failure and left ventricular dysfunction (LVD) have been reported. Most patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. In a phase 3 study of patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and LVD occurred in 0.7% of imatinib mesylate patients compared to 0.9% of IFN+Ara-C patients. In a study of newly diagnosed Ph+ CML patients in chronic phase comparing imatinib mesylate and nilotinib, cardiac failure was observed in 1.1% and 2.2% of patients, respectively, and severe (grade 3 or 4) cardiac failure occurred in 0.7% of patients in each group. Patients with cardiac disease, risk factors for cardiac disease, or history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated.

- Hepatotoxicity, occasionally severe, may occur. Cases of fatal liver failure and severe liver injury requiring liver transplants have been reported with both short-term and long-term use of imatinib mesylate. Assess liver function before initiation of treatment and monthly thereafter, or as clinically indicated. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. If severe hepatotoxicity occurs, imatinib mesylate should be withheld until the event has resolved and then resumed, depending on the initial severity of the event.

- When imatinib mesylate is combined with chemotherapy, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended.

- In the newly diagnosed CML trial of imatinib mesylate vs IFN+Ara-C, 1.8% of patients had grade 3/4 hemorrhage. In a study with newly diagnosed Ph+ CML patients in chronic phase comparing imatinib mesylate and nilotinib, gastrointestinal (GI) hemorrhage occurred in 1.4% of the patients in the imatinib mesylate arm and 2.9% of the patients in the nilotinib 300 mg twice daily arm. None of these events were grade 3 or 4 in the imatinib mesylate arm; 0.7% were grade 3 or 4 in the nilotinib arm. In addition, gastric antral vascular ectasia has been reported in postmarketing experience.

- Imatinib mesylate is sometimes associated with GI irritation. There have been rare reports, including fatalities, of GI perforation.

- In patients with hypereosinophilic syndrome with occult infiltration of HES cells within the myocardium, cardiogenic shock/LVD have been associated with HES cell degranulation upon initiation of imatinib mesylate therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporarily withholding imatinib mesylate. MDS/MPD disease and systemic mastocytosis may be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should be considered in patients with HES/CEL and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with imatinib mesylate should be considered at the initiation of therapy.

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- Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of imatinib mesylate at a lower dose, with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction.

- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib mesylate. TSH levels should be closely monitored in such patients.

- Fetal harm can occur when administered to a pregnant woman. Test pregnancy status in females of reproductive potential prior to imatinib mesylate initiation. Advise sexually active females of reproductive potential to avoid pregnancy and use effective contraception (methods that result in <1% pregnancy rates) when taking imatinib mesylate and for 14 days after stopping imatinib mesylate. Advise women to avoid breastfeeding during treatment and for 1 month after the last dose. If pregnancy occurs while taking imatinib mesylate, apprise the patient of the potential hazard to the fetus.

- Growth retardation has been reported in children and preadolescents receiving imatinib mesylate. The long-term effects of prolonged treatment with imatinib mesylate on growth in children are unknown; therefore, monitoring of growth in children taking imatinib mesylate is recommended.

- Cases of tumor lysis syndrome (TLS), including fatal cases, have been reported in patients with CML, ALL and eosinophilic leukemia receiving imatinib mesylate. The patients at risk for TLS are those with tumors having a high proliferative rate or high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken. Correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of imatinib mesylate.

- Motor vehicle accidents involving patients receiving imatinib mesylate have been reported. Advise patients that they may experience side effects such as dizziness, blurred vision, or somnolence during treatment with imatinib mesylate. Caution is recommended when driving a car or operating machinery.

- A decline in renal function may occur in patients receiving imatinib mesylate. Evaluate renal function at initiation and during therapy, with attention to risk factors for renal dysfunction such as preexisting renal impairment, diabetes mellitus, hypertension, and congestive heart failure.

- In Ph+ CML trials*, severe (grades 3/4) lab abnormalities included neutropenia (3.6%-48%), anemia (1%-42%), thrombocytopenia (<1%-33%), and hepatotoxicity (~5%). Severe (grades 3/4) adverse reactions experienced by Ph+ CML patients who received imatinib mesylate in clinical studies included hemorrhage (1.8%-19%), fluid retention (eg, pleural effusion, pulmonary edema, and ascites) (2.5%-11%), superficial edema (1.5%-6%), and musculoskeletal pain (2%-9%).† Severe fluid retention appears to be dose related, was more common in the advanced phase studies (where the dosage was 600 mg/day), and is more common in the elderly. In an additional study of patients with Ph+ CML in chronic phase comparing imatinib mesylate and nilotinib, severe (grades 3/4) adverse reactions and those with rates greater than 1% were diarrhea (4%), nausea (2%), and rash (2%).

- The safety profile for HES/CEL patients does not appear to be different from the safety profile of imatinib mesylate observed in other hematologic malignancy populations. All patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous, and musculoskeletal disorders. Hematologic abnormalities were also frequent, with instances of CTC Grade 3 leukopenia, neutropenia, lymphopenia, and anemia.

- For dermatofibrosarcoma (DFSP), severe (grades 3/4) lab abnormalities included anemia (17%), thrombocytopenia (17%), neutropenia (8%), and increased creatinine (8%).

- There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, acute respiratory failure, Hepatitis B virus reactivation and GI perforation.

- CYP3A4 is the major enzyme responsible for the metabolism of imatinib mesylate. Concomitant administration of imatinib mesylate and strong CYP3A4 inducers may reduce total exposure of imatinib mesylate; consider alternative agents. Concomitant administration of imatinib mesylate and strong CYP3A4 inhibitors may result in a significant imatinib mesylate exposure increase. Grapefruit juice should be avoided because it may increase plasma concentrations of imatinib mesylate. Imatinib mesylate will also increase plasma concentrations of other CYP3A4 metabolized drugs (eg, triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc). Use caution when administering imatinib mesylate with CYP3A4 and CYP2D6 substrates that have a narrow therapeutic window. Because warfarin is metabolized by CYP2C9 and CYP3A4, use low-molecular weight or standard heparin instead of warfarin in patients who require anticoagulation.

- Patients with moderate renal impairment (CrCL=20-39 mL/min) should receive a 50% decrease in the recommended starting dose; future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL=40-59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. Imatinib mesylate should be used with caution in patients with severe renal impairment.

- Isolated cases of imatinib mesylate overdose have been reported. In the event of overdosage, observe the patient and give appropriate supportive treatment.

Common Side Effects of imatinib mesylate Tablets

- Almost all adult Ph+ CML patients who received imatinib mesylate in clinical studies experienced adverse reactions at some time. In 4 Ph+ CML studies, the most frequently reported adverse reactions (all grades) and those with rates greater than 45% were superficial edema (60%-74%), nausea (50%-73%), diarrhea (43%-57%), hemorrhage (29%-53%), musculoskeletal pain (38%-49%), fatigue (30%-48%), rash and related terms (36%-47%), muscle cramps (28%-62%), and vomiting (23%-58%).† In an additional study of patients with newly diagnosed Ph+ CML in chronic phase comparing imatinib mesylate and nilotinib, the most frequently reported adverse reactions (all grades) and those with rates greater than 15% were diarrhea (46%), nausea (41%), muscle spasms (34%), vomiting (27%), headache (23%), nasopharyngitis (21%), fatigue (20%), peripheral edema (20%), rash (19%), myalgia (19%), eyelid edema (19%), arthralgia (17%), back pain (17%), and pain in extremity (16%).

- The adverse reactions and safety profile for Ph+ ALL, MDS/MPD, ASM, and HES/CEL were generally similar to the safety profile for Ph+ CML.

- The adverse reactions were similar for Ph+ ALL as for Ph+ CML. The most frequently reported drug-related adverse reactions in the Ph+ ALL studies were mild nausea, vomiting, diarrhea, myalgia, muscle cramps, and rash. Superficial edemas were also a common finding in all studies and were described primarily as periorbital or lower-limb edemas. However, these edemas were reported as grade 3/4 events in 6.3% of the patients and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of imatinib mesylate.

- Frequently reported adverse reactions (all grades) in the 7 MDS/MPD patients assessed were nausea (57%); diarrhea and muscle cramps (43% each); anemia, fatigue, arthralgia, and periorbital edema (29% each).

- All ASM patients experienced at least 1 adverse reaction at some time. The most frequently reported adverse reactions were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritus, rash, and lower respiratory tract infection

- All HES/CEL patients experienced at least 1 adverse reaction, the most common being GI, cutaneous, and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of CTC grade 3 leukopenia, neutropenia, lymphopenia, and anemia.

- Frequently reported adverse reactions (all grades) in the 12 DFSP patients assessed included nausea and fatigue (42% each); periorbital, peripheral, and eye edema (33% each); diarrhea, vomiting, rash, lacrimation increased, and anemia (25% each); face edema, pyrexia, exertional dyspnea, rhinitis, and anorexia (17% each).

- Supportive care may help reduce the severity of some mild to moderate adverse reactions. However, in some cases, either a dose reduction or interruption of treatment with imatinib mesylate may be necessary.

- Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered at 400 mg twice a day. For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron.

- Imatinib mesylate tablets should be taken with food and a large glass of water to minimize GI irritation.

- For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100 mg tablet, and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

- Patients should be instructed to take imatinib mesylate exactly as prescribed and not to change their dose or stop taking imatinib mesylate unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose.

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.

For more detailed study and product information, please see the Full Prescribing Information for Imatinib Mesylate Tablets. Additional information on Hikma US products is available on www.hikma.com/us.

†Numbers indicate the range of percentages in 4 studies among patients with newly diagnosed Ph+ CML, patients in blast crisis, in accelerated phase, and in the chronic phase after failure of interferon-alpha therapy.

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Document identification number: WW30007