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Press Release

Hikma launches Bosentan Tablets

London, 10 June 2019 – Hikma Pharmaceuticals PLC (Hikma, Group) (LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated Ba1 Moody's / BB+ S&P, both stable) the multinational pharmaceutical company, has launched Bosentan Tablets, 62.5mg and 125mg, the generic equivalent to Tracleer®[1], in the United States through its US affiliate, Hikma Pharmaceuticals USA Inc.[2]

Hikma's Bosentan is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).

In 2018 Actelion's US sales of Tracleer® (bosentan) were $268 million.[3]

Brian Hoffmann, President of Generics said, "We are pleased to add Bosentan Tablets to our US portfolio. This demonstrates our ability to develop technically challenging, differentiated medicines that address health issues impacting a growing number of people, bringing greater value to our customers and patients across the US."

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Enquiries

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[1] Tracleer® is a registered trademark of Actelion Pharmaceuticals Ltd.
[2] Hikma Pharmaceuticals USA Inc., formerly known as West-Ward Pharmaceuticals Corp.
[3] In 2017, Actelion Pharmaceuticals Ltd. was acquired by Johnson & Johnson. Sales figures were sourced from Johnson & Johnson's 2018 annual report.

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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 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'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 8,400 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 Bosentan Tablets, 62.5mg and 125mg:

BOXED WARNING: RISKS OF HEPATOTOXICITY and EMBRYO-FETAL TOXICITY
See full Prescribing Information.

Because of the risks of hepatotoxicity and birth defects, Bosentan is available only through a restricted program called the bosentan REMS Program. The bosentan REMS Program is a component of the bosentan Risk Evaluation and Mitigation Strategy (REMS). Under the bosentan REMS Program, prescribers, patients, and pharmacies must enroll in the program.

Hepatotoxicity

In clinical studies, bosentan caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious hepatotoxicity, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly.

In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with bosentan in patients with multiple comorbidities and drug therapies. There have also been reports of liver failure. The contribution of bosentan in these cases could not be excluded.

In at least one case, the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of bosentan. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping bosentan with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction.

Elevations in aminotransferases require close attention. Bosentan should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring for hepatotoxicity may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥2 x ULN, treatment with bosentan should be stopped. There is no experience with the reintroduction of bosentan in these circumstances.

Embryo-Fetal Toxicity

Bosentan is likely to cause major birth defects if used by pregnant females based on animal data. Therefore, pregnancy must be excluded before the start of treatment with bosentan. Throughout treatment

and for one month after stopping bosentan, females of reproductive potential must use two reliable methods of contraception unless the patient has an intrauterine device (IUD) or tubal sterilization, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving bosentan. Obtain monthly pregnancy tests.

Contraindications
Bosentan is contraindicated:

- In females who are or may become pregnant.
- For use with cyclosporine A.
- For use with glyburide.
- In patients who are hypersensitive to bosentan or any component of the product. Observed reactions include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), anaphylaxis, rash and angioedema.

Warnings and Precautions
Hepatotoxicity
In clinical studies, ALT or AST >3 x ULN were observed in 11% of bosentan-treated patients (n=658) compared to 2% of placebo-treated patients (n=280), accompanied by elevated bilirubin in a small number of cases (2 of 658). The combination of hepatocellular injury (increases in aminotransferases of >3 x ULN) and increases in total bilirubin (≥2 x ULN) is a marker for potential serious hepatotoxicity. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly and therapy adjusted accordingly. Discontinue bosentan if liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN. Avoid using bosentan in patients with moderate or severe liver impairment or elevated ALT or AST >3 x ULN prior to drug initiation. In WHO Functional Class II patients, consider whether the benefits of bosentan are sufficient to offset the risk of hepatotoxicity, which may preclude future use as their disease progresses.

Embryo-fetal Toxicity
Based on data from animal reproduction studies, bosentan may cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. Advise females of reproductive potential of the potential risk to a fetus. Obtain a pregnancy test prior to bosentan treatment, monthly during treatment and for one month after stopping treatment. Advise females of reproductive potential to use two reliable forms of contraception during treatment with bosentan and for at least one month after the last dose. Because of the risks of hepatotoxicity and birth defects, bosentan is available only through a restricted program called the bosentan REMS Program.

Prescribing and Distribution Program for Bosentan
Because of the risks of hepatotoxicity and birth defects, bosentan is available only through a restricted program called the bosentan REMS Program. Further information about bosentan and the bosentan REMS Program is available at www.bosentanREMSProgram.com or 1-866-359-2612.

Fluid Retention
If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as bosentan or underlying heart failure, and the possible need for treatment or discontinuation of bosentan.

Pulmonary Veno-Occlusive Disease
If signs of pulmonary edema occur, consider the possibility of associated pulmonary veno-occlusive disease and consider whether bosentan should be discontinued.

Decreased Sperm Counts
Decreased sperm counts have been observed in patients receiving bosentan. Preclinical data also suggest that bosentan, like other endothelin receptor antagonists, may have an adverse effect on spermatogenesis.

Decreases in Hemoglobin and Hematocrit

Treatment with bosentan can cause a dose-related decrease in hemoglobin (Hgb) and hematocrit, which can result in anemia requiring transfusion. Hgb concentration should be checked after 1 and 3 months and every 3 months thereafter. If a marked decrease in Hgb concentration occurs, evaluate to determine the cause and need for specific treatment.

Adverse Events
In clinical trials, the most common adverse events occurring more often in bosentan-treated patients than in patients taking placebo were respiratory tract infection (22% vs 17%), headache (15% vs 14%), edema (11% vs 9%), chest pain (5% vs 5%), syncope (5% vs 4%), flushing (4% vs 3%), hypotension (4% vs 2%), sinusitis (4% vs 2%), arthralgia (4% vs 2%), abnormal serum aminotransferases (4% vs 2%), palpitations (4% vs 2%) and anemia (3% vs 0%).

Drug Interactions
- Bosentan is contraindicated for use with cyclosporine A and with glyburide.

- Bosentan is metabolized by CYP2C9 and CYP3A.
    - Co-administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A inhibitor (eg, ketoconazole, itraconazole) or a moderate CYP3A inhibitor (eg, amprenavir, erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor with bosentan is not recommended.
    - Hormonal contraceptives, including oral, injectable, transdermal and implantable forms, may not be reliable when bosentan is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking bosentan.
    - When initiating lopinavir/ritonavir and other ritonavir-containing HIV regimens, dosage adjustment of bosentan is necessary.
    - When co-administered with simvastatin or other statins that are CYP3A substrates, dosage adjustment of such statins may need to be considered. Cholesterol should be monitored.
    - When co-administered with rifampin, a CYP3A inducer, liver function should be monitored weekly.
    - When co-administered with ketoconazole, a potent CYP3A inhibitor, no dose adjustment of bosentan is necessary, but increased effects of bosentan may need to be considered.

Monitoring
It is important to adhere strictly to the monthly monitoring schedule for aminotrasferases and bilirubin levels and, if applicable, pregnancy for the duration of treatment.

Generic bosentan is subject to a REMS (Risk Evaluation and Mitigation Strategies) that is required by FDA for all pharmaceutical companies that manufacture and market any bosentan product. Please visit https://www.bosentanremsprogram.com for more information regarding the Bosentan REMS Program.

For more information, please see the full Prescribing Information, including the Boxed Warning about hepatotoxicity and embryo-fetal toxicity.

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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