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Press Release

Hikma expands generics portfolio with Everolimus Tablets launch

London, March 13, 2020 – Hikma Pharmaceuticals PLC (Hikma, Group), the multinational generic pharmaceutical company, has launched Everolimus Tablets, 0.25mg, 0.50mg and 0.75mg, the generic equivalent to Zortress®,[1] in the United States through its US affiliate, Hikma Pharmaceuticals USA Inc.

"We are very pleased to be providing patients and health care providers in the US with a generic version of this important medicine," said Brian Hoffmann, President of Generics. "The launch of Everolimus Tablets expands our diversified portfolio of generic medicines in the US and, as a paragraph IV product, demonstrates our ability to successfully litigate and bring greater value to our customers and patients in the US."

According to IQVIA, US sales of Everolimus Tablets, 0.25mg, 0.50mg and 0.75mg, were approximately $150 million in the 12 months ending January 2020.

Everolimus Tablets are indicated for:

1. **Prophylaxis of Organ Rejection in Kidney Transplantation**
   Everolimus is indicated for the prophylaxis of organ transplantation in adult patients at low-moderate immunologic risk receiving a kidney transplant. Everolimus is to be administered in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and with corticosteroids. Therapeutic drug monitoring (TDM) of Everolimus and cyclosporine is recommended for all patients receiving these products.

2. **Prophylaxis of Organ Rejection in Liver Transplantation**
   Everolimus is indicated for the prophylaxis of allograft rejection in adult patients receiving a liver transplant. Everolimus is to be administered no earlier than 30 days posttransplant concurrently in combination with reduced doses of tacrolimus and with corticosteroids. TDM of Everolimus and cyclosporine is recommended for all patients receiving these products.

- ENDS -

Enquiries

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[1] Zortress® is a registered trademark of Novartis AG

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated Ba1/stable Moody's and BB+/positive 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-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 Everolimus Tablets, 0.25mg, 0.50mg and 0.75mg:

BOXED WARNING: MALIGNANCIES AND SERIOUS INFECTIONS, KIDNEY GRAFT THROMBOSIS; NEPHROTOXICITY; AND MORTALITY IN HEART TRANSPLANTATION

Malignancies and Serious Infections

- **Only physicians experienced in immunosuppressive therapy and management of transplant patients should prescribe Everolimus. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.**

- **Increased susceptibility to infection and the possible development of malignancies such as lymphoma and skin cancer may result from immunosuppression.**

Kidney Graft Thrombosis

- **An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, was reported, mostly within the first 30 days posttransplantation.**

Nephrotoxicity

- **Increased nephrotoxicity can occur with use of standard doses of cyclosporine in combination with Everolimus. Therefore, reduced doses of cyclosporine should be used in combination with Everolimus in order to reduce renal dysfunction. It is important to monitor the cyclosporine and Everolimus whole blood trough concentrations.**

Mortality in Heart Transplantation

- **Increased mortality, often associated with serious infections, within the first three months posttransplantation was observed in a clinical trial of *de novo* heart transplant patients**

receiving immunosuppressive regimens with or without induction therapy. Use in heart transplantation is not recommended.

CONTRAINDICATIONS

Everolimus is contraindicated in patients with known hypersensitivity to Everolimus, sirolimus or to components of the drug product.

WARNINGS AND PRECAUTIONS

- **Management of Immunosuppression**

Only physicians experienced in management of systemic immunosuppressant therapy in transplantation should prescribe or oversee maintenance therapy with Everolimus. In limited data with the complete elimination of calcineurin inhibition, there was an increased risk of acute rejection.

- **Lymphomas and Other Malignancies**

Patients receiving immunosuppressants, including Everolimus, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

- **Serious Infections**

Patients receiving immunosuppressants, including Everolimus, are at increased risk of developing bacterial, viral, fungal and protozoal infections (including opportunistic infections), which may lead to serious, even fatal, outcomes. Combination immunosuppressant therapy should be used with caution due to danger of over-immunosuppression. For additional recommendations, see the full Prescribing Information for Everolimus tablets.

- **Kidney Graft Thrombosis**

An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, has been reported, usually within the first 30 days posttransplantation.

- **Hepatic Artery Thrombosis (HAT)**

Do not administer Everolimus earlier than 30 days after liver transplant due to risk of HAT.

- **Everolimus and Calcineurin Inhibitor-Induced Nephrotoxicity**

Monitor renal function during administration of Everolimus. In patients receiving cyclosporine, a reduced dose should be used to reduce renal dysfunction. In patients receiving tacrolimus, a reduced dose should be used to minimize the potential risk of nephrotoxicity. Consider switching to other immunosuppressive therapies if renal function does not improve after dose adjustments or if the dysfunction is thought to be drug-related. Caution should be exercised when using other drugs which are known to impair renal function.

- **Heart Transplantation**

Use of Everolimus in heart transplantation is not recommended due to increased risk of infection-related mortality.

- **Angioedema**

Everolimus has been associated with the development of angioedema and may increase this risk when used in combination with other drugs known to cause angioedema.

- **Wound Healing and Fluid Accumulation**

Everolimus increases the risk of delayed wound healing and increases the occurrence of wound-related complications. Generalized fluid accumulation and localized fluid collection have also been reported.

- **Interstitial Lung Disease (ILD)/Non-Infectious Pneumonitis**

Cases of ILD, some reported with pulmonary hypertension as a secondary event, have occurred in patients receiving rapamycins and their derivatives, including Everolimus. Though most cases generally resolve on drug interruption and with or without glucocorticoid therapy, some fatal cases have occurred.

- **Hyperlipidemia**

All patients receiving Everolimus should be monitored for hyperlipidemia. Increased serum cholesterol and triglycerides have been reported to occur. Use of anti-lipid therapy may not normalize lipid levels in patients receiving Everolimus.

Due to an interaction with cyclosporine, concomitant treatment with HMG-CoA reductase inhibitors simvastatin and lovastatin is strongly discouraged. For details, see the full Prescribing Information for Everolimus tablets.

- **Proteinuria**

Patients receiving Everolimus should be monitored for proteinuria.

- **Polyoma Virus Infections**

Patients receiving immunosuppressants, including Everolimus, are at increased risk for opportunistic infections, including polyoma virus infections, which may have serious and even fatal outcomes in transplant patients. For details, see the full Prescribing Information for Everolimus tablets.

- **Interaction with Strong Inhibitors and Inducers of CYP3A4**

Coadministration of Everolimus with strong CYP3A4 inhibitors and strong CYP3A4 inducers is not recommended without close monitoring of Everolimus whole blood trough concentrations.

- **Thrombotic Microangiopathy/Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TMA/TTP/HUS)**

The concomitant use of Everolimus with cyclosporine may increase the risk of TMA/TTP/HUS; monitor hematologic parameters.

- **New Onset Diabetes After Transplant**

Monitor blood glucose concentrations closely in patients receiving Everolimus, as it has been shown to increase the risk of new onset diabetes after transplant.

- **Embryo-Fetal Toxicity**

Everolimus may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to avoid becoming pregnant and to use effective contraception while using Everolimus and for 8 weeks after ending treatment.

- **Male Infertility**

Azospernia or oligospermia may be observed.

- **Immunizations**

Advise patients to avoid immunization with live vaccines during treatment with Everolimus.

- **Interaction With Grapefruit Juice**

Advise patients receiving Everolimus and cyclosporine or tacrolimus to avoid consuming grapefruit and grapefruit juice during treatment.

- **Patients With Heredity Disorders/Other**

Patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Everolimus.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in detail in the full Prescribing Information for Everolimus tablets:

- Hypersensitivity reactions
- Lymphomas and other malignancies
- Serious infections
- Kidney graft thrombosis
- Hepatic Artery Thrombosis
- Everolimus and calcineurin inhibitor-induced nephrotoxicity
- Heart transplantation
- Angioedema
- Wound healing and fluid accumulation
- Interstitial Lung Disease /Non-infectious pneumonitis
- Hyperlipidemia
- Proteinuria
- Polyoma Virus Infections
- Thrombotic Microangiopathy/Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TMA/TTP/HUS) New onset diabetes after transplant
- Male infertility

The most common (≥20%) adverse reactions observed in patients treated with Everolimus in a kidney transplantation trial were: peripheral edema, constipation, hypertension, nausea, anemia, urinary tract infection and hyperlipidemia.

The most common (≥10%) adverse reactions observed in patients treated with Everolimus in a liver transplantation trial were: diarrhea, headache, peripheral edema, hypertension, nausea, pyrexia, abdominal pain and leukopenia.

DRUG INTERACTIONS

- Caution should be exercised when co-administering Everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index.
- Dose adjustment of Everolimus may be needed if the cyclosporine dose is altered. Everolimus has a clinically minor influence on cyclosporine pharmacokinetics.
- Strong inhibitors of CYP3A4 should not be co-administered with Everolimus.
- If erythromycin is coadministered, Everolimus blood concentrations should be monitored and the dose adjusted as necessary.
- If verapamil is coadministered, Everolimus blood concentrations should be monitored and the dose adjusted as necessary.
- Patients taking atorvastatin (CYP3A4 substrate) and pravastatin (P-gp substrate) should be monitored for the development of rhabdomyolysis and other adverse reactions associated with these products.
- The use of HMG-CoA reductase inhibitors is strongly discouraged in kidney transplant patients taking Everolimus with cyclosporine.
- Combination therapy with rifampin is not recommended.
- Moderate inhibitors of CYP3A4 and P-gp may increase Everolimus blood concentrations.
- Coadministration of Everolimus and depot octreotide increased octreotide C_{min} by approximately 50%.

USE IN SPECIFIC POPULATIONS

Pregnancy

Everolimus can cause fetal harm when administered to a pregnant woman.

Lactation

Advise women not to breastfeed because of the potential for serious adverse reactions in infants exposed to Everolimus.

Females and Males of Reproductive Potential
Females of reproductive potential are recommended to use highly effective contraception methods while receiving Everolimus and up to 8 weeks after stopping treatment.

Pediatric Patients
The safe and effective use of Everolimus in kidney or liver transplant patients younger than 18 years of age has not been established.

Geriatric Use
There is limited clinical experience on the use of Everolimus in patients aged 65 or older.

Hepatic Impairment
Everolimus dose adjustments are needed and whole blood trough concentrations should be closely monitored in patients with hepatic impairment. For details, see the full Prescribing Information for Everolimus tablets.

INDICATIONS AND USAGE

1. **Prophylaxis of Organ Rejection in Kidney Transplantation**
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Limitations of Use
The safety and efficacy of Everolimus has not been established in the following populations:

- Kidney transplant patients at high immunologic risk
- Recipients of transplanted organs other than kidney and liver

Pediatric patients (less than 18 years)

For more information, please see the Medication Guide and full Prescribing Information, including the Boxed Warning.

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

Manufactured by: West-Ward Columbus Inc., Columbus, OH 43228
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