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Press Release

Hikma launches Rufinamide Oral Suspension, 40 mg/mL

London, 4 November, 2020 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Rufinamide Oral Suspension, 40mg/mL, the generic version of Banzel®[1] in the US through its US affiliate, Hikma Pharmaceuticals USA Inc.

Rufinamide Oral Suspension is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in pediatric patients 1 year of age and older and in adults.

According to IQVIA, US sales of Rufinamide Oral Suspension, 40mg/mL, were approximately $125 million in the 12 months ending September 2020.

“We are very pleased to launch a generic version of this important medicine in the US,” said Brian Hoffmann, President of Hikma Generics. "This launch further diversifies our portfolio of products and demonstrates our ability to successfully litigate patents, improving patients’ access to high-quality medicines.”

- ENDS -

Enquiries

Hikma Pharmaceuticals PLC

Susan Ringdal
EVP, Strategic Planning and Global Affairs
+44 (0)20 7399 2760/ +44 7776 477050
uk-investors@hikma.uk.com

Steve Weiss
David Belian
US Communications and Public Affairs
+1 732 720 2830/ +1 732 788 8279
+1 732 720 2814/+1 848 254 4875
uscommunications@hikma.com

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

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

[1] Banzel® is a registered trademark of Novartis AG.

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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 Rufinamide Oral Suspension, 40mg/mL:

CONTRAINDICATIONS
Rufinamide is contraindicated in patients with Familial Short QT syndrome.

WARNINGS AND PRECAUTIONS

- **Suicidal Behavior and Ideation**

Antiepileptic drugs (AEDs), including rufinamide, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy; median treatment duration of 12 weeks) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk of suicidal thinking or behavior compared to patients randomized to placebo. There were four suicides in the drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed.

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing rufinamide or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. For more information, see the full Prescribing Information for Rufinamide oral solution.

- **Central Nervous System Reactions**

Use of rufinamide has been associated with central nervous system-related adverse reactions in the controlled clinical trial of patients 4 years or older with Lennox-Gastaut Syndrome. The most significant of these can be classified into two general categories: 1) somnolence or fatigue and 2) coordination abnormalities, dizziness, gait disturbance and ataxia.

Patients should be advised not to drive or operate machinery until they have gained sufficient experience on rufinamide to gauge whether it adversely affects their ability to drive or operate machinery.

- **QT Shortening**

Formal cardiac ECG studies demonstrated shortening of the QT interval (mean=20 msec, for doses ≥2400 mg twice daily) with rufinamide.

Reductions of the QT interval below 300 msec were not observed in the formal QT studies with doses up to 7200 mg/day. Moreover, there was no signal for drug-induced sudden death or ventricular arrhythmias.

The degree of QT shortening induced by rufinamide is without any known clinical risk. Familial Short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in this syndrome are believed to occur primarily when the corrected QT interval falls below 300 msec. Non-clinical data also indicate that QT shortening is associated with ventricular fibrillation.

Patients with Familial Short QT syndrome should not be treated with rufinamide. Caution should be used when administering rufinamide with other drugs that shorten the QT interval.

- **Multi-organ Hypersensitivity/Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)**

DRESS, also known as multi-organ hypersensitivity, has been reported in patients taking antiepileptic drugs, including rufinamide. DRESS may be fatal or life-threatening. It is important to note that early manifestations of hypersensitivity may be present even though symptoms are not evident.

If DRESS is suspected, the patient should be evaluated immediately, rufinamide should be discontinued and alternative treatment should be started.

- **Withdrawal of AEDs**

As with all antiepileptic drugs, rufinamide should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation or status epilepticus. If abrupt discontinuation of the drug is medically necessary, the transition to another AED should be made under close medical supervision.

- **Status Epilepticus**

Estimates of the incidence of treatment-emergent status epilepticus among patients treated with rufinamide are difficult because standard definitions were not employed.

In all controlled trials that included patients with different epilepsies, 11 of 1240 (0.9%) rufinamide-treated patients had episodes that could be described as status epilepticus, compared with none of the 635 placebo-treated patients.

- **Leukopenia**

Rufinamide has been shown to reduce white cell count.

ADVERSE REACTIONS

The following serious adverse reactions are described in the full Prescribing Information for Rufinamide oral suspension:

- Suicidal Behavior or Ideation
- Central Nervous System Reactions
- QT Shortening
- Multi-Organ Hypersensitivity/Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)
- Leukopenia

In the pooled, double-blind, adjunctive therapy studies in adult and pediatric patients ages 3 to 17, the most common (≥10%) adverse reactions in rufinamide-treated patients, in all doses studied (200 to 3200 mg per day) with a higher frequency than in patients on placebo were: headache, dizziness, fatigue, somnolence and nausea. For more information, see the full Prescribing Information for Rufinamide oral solution.

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DRUG INTERACTIONS

- **Effects of Rufinamide on Other AEDs**

Population pharmacokinetic analysis of average concentration at steady state of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate and valproate showed that typical rufinamide C_{avss} levels had little effect on the pharmacokinetics of other AEDs. Any effects, when they occur, have been more marked in the pediatric population.

The decrease in clearance of phenytoin estimated at typical rufinamide levels is predicted to increase plasma levels of phenytoin by 7% to 21%. As phenytoin is known to have non-linear pharmacokinetics, it is possible that exposure will be greater than the model prediction.

For more information about the effects of rufinamide on other AEDs, see the full Prescribing Information for Rufinamide oral solution.

- **Effects of Other AEDs on Rufinamide**

Potent cytochrome P450 enzyme inducers, such as carbamazepine, phenytoin, primidone and phenobarbital, appear to increase the clearance of rufinamide. Any effects, where they occurred, were likely to be more marked in the pediatric population.

Patients stabilized on rufinamide before being prescribed valproate should begin valproate therapy at a low dose. Similarly, patients on valproate should begin rufinamide therapy at a dose lower than 10 mg/kg/day (pediatric patients) or 400 mg/day (adults).

For more information about the effects of other AEDs on rufinamide, see the full Prescribing Information for Rufinamide oral solution.

- **Effects of Rufinamide on Hormonal Contraceptives**

Female patients of childbearing age should be warned that the concurrent use of rufinamide with hormonal contraceptives may render this method of contraception less effective. Additional non-hormonal forms of contraception are recommended when using rufinamide.

USE IN SPECIFIC POPULATIONS

- **Pregnancy**

There are no adequate data on the developmental risks associated with use of rufinamide in pregnant women. Encourage women who are taking rufinamide during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org.

- **Lactation**

There are no data on the presence of rufinamide in human milk, the effects on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for rufinamide and any potential adverse effects on the breastfed infant from rufinamide or from the underlying maternal condition.

- **Females and Males of Reproductive Potential**

Use of rufinamide may reduce the effectiveness of hormonal contraceptives containing ethinyl estradiol or norethindrone. Advise women of reproductive potential taking rufinamide who are using a contraceptive containing ethinyl estradiol and norethindrone to use an additional non-hormonal form of contraception.

The effect of rufinamide on fertility in humans has not been established.

- **Pediatric Use**

Safety and effectiveness have been established in pediatric patients 1 to 17 years of age. Safety and

effectiveness in pediatric patients younger than 1 year have not been established.

- **Geriatric Use**

Clinical studies of rufinamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

- **Renal Impairment**

Rufinamide pharmacokinetics in patients with severe renal impairment (creatinine clearance <30 mL/min) was similar to that of healthy subjects. Dose adjustment in patients undergoing dialysis should be considered.

- **Hepatic Impairment**

Use of rufinamide in patients with severe hepatic impairment (Child-Pugh score 10 to 15) is not recommended. Caution should be exercised in treating patients with mild (Child-Pugh score 5 to 6) to moderate (Child-Pugh score 7 to 9) hepatic impairment.

DOSAGE AND ADMINISTRATION

- **Administration Information**

Administer rufinamide with food.

- **Dosing in Patients Undergoing Dialysis**

Consider adjusting the rufinamide dose during hemodialysis, as the dialysis process may reduce exposure to a limited (about 30%) extent.

- **Dosing in Patients With Hepatic Disease**

The use of rufinamide in patients with severe hepatic impairment is not recommended. Use caution when treating patients with mild to moderate hepatic impairment.

- **Dosing in Patients Taking Valproate**

Patients taking valproate should begin rufinamide at a lower dose (<10 mg/kg per day in pediatric patients; 400 mg/day in adults).

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

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.

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