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Press Release

Hikma launches authorized generic of Xyrem® (sodium oxybate) in the US

London, 3 January 2023 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces it has launched an authorized generic version of Jazz Pharmaceuticals' Xyrem®[1] (sodium oxybate) oral solution CIII. Hikma will have 180 days of marketing exclusivity for its authorized generic product in the US.

Sodium Oxybate oral solution, 0.5 g/mL is a prescription medicine used to treat the following symptoms in people 7 years of age or older with narcolepsy:

- sudden onset of weak or paralyzed muscles (cataplexy)
- excessive daytime sleepiness (EDS)

Jazz Pharmaceuticals reported net sales for Xyrem® of $1.3 billion in 2021.

Brian Hoffmann, President of Generics said, "We are pleased to be able to provide the first authorized generic version of Xyrem® to patients and health care providers in the US. This launch further expands our diversified portfolio of generic products, and underscores our ability to put Better Health, Within Reach, Every Day®[2] for the millions of people who rely on our medicines."

- ENDS -

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

Hikma helps put better health within reach every day for millions of people 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 8,700 colleagues are helping to shape a healthier

[1] Xyrem® is a registered trademark of JAZZ PHARMACEUTICALS, INC.
[2] Better Health. Within Reach. Every Day® is a registered trademark of Hikma Pharmaceuticals PLC.

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

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

• Central Nervous System Depression
Sodium Oxybate Oral Solution is a Central Nervous System (CNS) depressant. In clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in adult patients treated with Sodium Oxybate Oral Solution. Many patients who received Sodium Oxybate Oral Solution during clinical trials in narcolepsy were receiving CNS stimulants.

• Abuse and Misuse
Sodium Oxybate Oral Solution is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.

Because of the risks of CNS depression and abuse and misuse, Sodium Oxybate Oral Solution is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS.

Contraindications
Sodium Oxybate Oral Solution is contraindicated for use in:
• combination with sedative hypnotics or alcohol
• patients with succinic semialdehyde dehydrogenase deficiency.

Warnings and Precautions
Central Nervous System Depression
The concurrent use of Sodium Oxybate Oral Solution with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with Sodium Oxybate Oral Solution is required, dose reduction or discontinuation of one or more CNS depressants (including Sodium Oxybate Oral Solution) should be considered. In addition, if short-term use of an opioid (eg, post- or perioperative) is required, interruption of treatment with Sodium Oxybate Oral Solution should be considered.

After first initiating treatment and until certain that Sodium Oxybate Oral Solution does not affect them adversely (eg, impair judgment, thinking, or motor skills), caution patients against hazardous activities requiring complete mental alertness or motor coordination such as operating hazardous machinery, including automobiles or airplanes. Also caution patients against these hazardous activities for at least 6 hours after taking Sodium Oxybate Oral Solution. Patients should be queried about CNS depression related events upon initiation of Sodium Oxybate Oral Solution therapy and periodically thereafter.

Abuse and Misuse
Sodium Oxybate Oral Solution is a Schedule III controlled substance. The active ingredient of Sodium Oxybate Oral Solution, sodium oxybate or gamma hydroxybutyrate (GHB), is a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of Sodium Oxybate Oral Solution, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (eg, assault victim). Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

XYWAV and XYREM REMS
Because of the risks of central nervous system depression and abuse/misuse, Sodium Oxybate Oral

Solution is available only through a restricted distribution program called the XYWAV and XYREM REMS.
Notable requirements of the XYWAV and XYREM REMS include the following:
• Healthcare Providers who prescribe Sodium Oxybate Oral Solution are specially certified
• Sodium Oxybate Oral Solution will be dispensed only by the central pharmacy that is specially certified
• Sodium Oxybate Oral Solution will be dispensed and shipped only to patients who are enrolled in the XYWAV and XYREM REMS with documentation of safe use
Further information is available at www.XYWAVXYREMREMS.com or 1-866-997-3688.

Respiratory Depression and Sleep-Disordered Breathing
Sodium Oxybate Oral Solution may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported. Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with Sodium Oxybate Oral Solution administration in adult and pediatric patients. Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy and among patients with narcolepsy.

Depression and Suicidality
In adult clinical trials in patients with narcolepsy (n=781), there were two suicides and two attempted suicides in Sodium Oxybate Oral Solution - treated patients, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used Sodium Oxybate Oral Solution in conjunction with other drugs. Sodium Oxybate Oral Solution was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 Sodium Oxybate Oral Solution - treated patients, with four patients (<1%) discontinuing because of depression. In most cases, no change in Sodium Oxybate Oral Solution treatment was required. In the pediatric clinical trial in patients with narcolepsy (n=104), one patient experienced suicidal ideation and two patients reported depression while taking Sodium Oxybate Oral Solution. The emergence of depression in patients treated with Sodium Oxybate Oral Solution requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking Sodium Oxybate Oral Solution.

Other Behavioral or Psychiatric Adverse Reactions
During adult clinical trials in narcolepsy, 3% of 781 patients treated with Sodium Oxybate Oral Solution experienced confusion, with incidence generally increasing with dose. In a controlled trial in adults where patients were randomized to fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the majority of cases in all adult clinical trials in patients with narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment.

Anxiety occurred in 5.8% of the 874 patients receiving Sodium Oxybate Oral Solution in adult clinical trials in another population. Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy and the post-marketing setting included hallucinations, paranoia, psychosis, aggression, and agitation. In the pediatric clinical trial in patients with narcolepsy, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety, were reported while taking Sodium Oxybate Oral Solution. The emergence or increase of behavioral or psychiatric events in adult and pediatric patients taking Sodium Oxybate Oral Solution should be carefully monitored.

Parasomnias
Instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of Sodium Oxybate Oral Solution in adult patients with narcolepsy. Parasomnias, including sleepwalking, also have been reported in the pediatric clinical trial and in postmarketing experience with Sodium Oxybate Oral Solution. Episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

Use in Patients Sensitive to High Sodium Intake
Sodium Oxybate Oral Solution has a high salt content. In patients sensitive to salt intake (eg, those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of Sodium Oxybate Oral Solution.

Most Common Adverse Reactions
In three controlled adult clinical trials in patients with narcolepsy, the most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in Sodium Oxybate Oral Solution - treated patients were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

In the pediatric clinical trial in pediatric patients 7 years of age and older with narcolepsy, the most common adverse reactions (≥5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%) and sleepwalking (6%). The overall adverse reaction profile of Sodium Oxybate Oral Solution in the pediatric clinical trial was similar to that seen in the adult clinical trial program.

Additional safety information is required when full promotional messages are presented:

Additional Adverse Reactions
Additional adverse reactions that occurred in ≥2% of patients in any treatment group for three controlled adult trials and were more frequent in any Sodium Oxybate Oral Solution treatment group than with placebo were diarrhea, upper abdominal pain, dry mouth, pain, feeling drunk, peripheral edema, cataplexy, muscle spasms, extremity pain, attention disturbance, paresthesia, sleep paralysis, disorientation, irritability, sleepwalking, anxiety and hyperhidrosis.

Discontinuation: Of the 398 Sodium Oxybate Oral Solution - treated adult patients with narcolepsy, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment. In the pediatric clinical trial, 7 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; affect lability; anger, anxiety, depression; and headache).

Dose-Response Information: In clinical trials in adult patients with narcolepsy, a dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking, and enuresis. The incidence of all these reactions was notably higher at 9 g per night. In controlled trials in adults with narcolepsy, discontinuations of treatment due to adverse reactions were greater at higher doses of Sodium Oxybate Oral Solution.

Drug Interactions
Sodium Oxybate Oral Solution is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of Sodium Oxybate Oral Solution.

Concomitant use of Sodium Oxybate Oral Solution with divalproex sodium resulted in a 25% mean increase in systemic exposure to GHB and in a greater impairment on some tests of attention and working memory. An initial dose reduction of Sodium Oxybate Oral Solution is recommended when used concomitantly with divalproex sodium. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of Sodium Oxybate Oral Solution and divalproex sodium is warranted.

Pregnancy and Lactation
There are no adequate data on the developmental risk associated with the use of sodium oxybate in pregnant women. Sodium Oxybate Oral Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sodium Oxybate Oral Solution and any potential adverse effects on the breastfed infant from Sodium Oxybate Oral Solution or from the underlying maternal condition.

Pediatric Use
Safety and effectiveness of Sodium Oxybate Oral Solution in pediatric patients below the age of 7 years have not been established.

Geriatric Use
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.

Hepatic Impairment
The starting dose of Sodium Oxybate Oral Solution should be reduced in patients with liver impairment. **Dosage Modification in Patients with Hepatic Impairment:** The recommended starting dosage in patients with hepatic impairment is one-half of the original dosage per night, administered orally divided into two doses.

Dependence and Tolerance
There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of Sodium Oxybate Oral Solution have not been systematically evaluated in controlled clinical trials.

In the clinical trial experience with Sodium Oxybate Oral Solution in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

Tolerance to Sodium Oxybate Oral Solution has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended Sodium Oxybate Oral Solution dosage regimen.

Document identification number: HK-1970-v1