Press Release

Hikma launches Ephedrine Sulfate Injection, USP

London, 4 February 2021 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Ephedrine Sulfate Injection, USP, 50mg/mL, in the US, through its US affiliate, Hikma Pharmaceuticals USA Inc.

Ephedrine Sulfate Injection, USP is an alpha- and beta- adrenergic agonist and a norepinephrine releasing agent indicated for the treatment of clinically important hypotension occurring in the setting of anaesthesia.

According to IQVIA, US sales of Ephedrine Sulfate Injection, USP, 50mg/mL, were approximately $64 million in the 12 months ending November 2020.

Hikma is the third largest US supplier of generic injectable medicines by volume, with a growing portfolio of over 100 products. Today one in every six injectable generic medicines used in US hospitals is a Hikma product.

- ENDS -

Enquiries

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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 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

hikma.

Important Safety Information for Ephedrine Sulfate Injection, USP, 50mg/mL:

CONTRAINDICATIONS

None.

WARNINGS & PRECAUTIONS

- **Pressor Effects with Concomitant Use with Oxytocic Drugs:** serious postpartum hypertension has been described in patients who received both a vasopressor (i.e., methoxamine, phenylephrine, ephedrine) and an oxytocic (i.e., methylergonovine, ergonovine). Some of these patients experienced a stroke. Carefully monitor the blood pressure of individuals who have received both ephedrine and an oxytocic.
- **Tachyphylaxis and Tolerance:** data indicate that repeated administration of ephedrine can result in tachyphylaxis. Clinicians treating anesthesia-induced hypotension with Ephedrine Sulfate Injection, USP should be aware of the possibility of tachyphylaxis and should be prepared with an alternative pressor to mitigate unacceptable responsiveness.
- **Risk of Hypertension When Used Prophylactically:** when used to prevent hypotension, ephedrine has been associated with an increased incidence of hypertension compared with when ephedrine is used to treat hypotension.

ADVERSE REACTIONS

Most common adverse reactions during treatment: nausea, vomiting, and tachycardia.

The following adverse reactions associated with the use of ephedrine sulfate were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Gastrointestinal disorders: Nausea, vomiting

Cardiac disorders: Tachycardia, palpitations (thumping heart), reactive hypertension, bradycardia, ventricular ectopics, R-R variability (heart rate variability).

Nervous system disorders: Dizziness.

Psychiatric disorders: Restlessness.

DRUG INTERACTIONS

Interactions that Augment the Pressor Effect

- **Oxytocin and oxytocic drugs:** serious postpartum hypertension has been described in patients who received both a vasopressor (i.e., methoxamine, phenylephrine, ephedrine) and an oxytocic (i.e., methylergonovine, ergonovine). Some of these patients experienced a stroke.
- **Clonidine, propofol, monoamine oxidase inhibitors (MAOIs), atropine:** these drugs augment the pressor effect of ephedrine.

Interactions that Antagonize the Pressor Effect

- **Ex. α-adrenergic antagonists, β-adrenergic receptor antagonists, reserpine, quinidine, mephentermine**: these drugs antagonize the pressor effect of ephedrine.

Other Drug Interactions

- **Guanethidine:** Ephedrine may inhibit the neuron blockage produced by guanethidine, resulting in loss of antihypertensive effectiveness.
- **Rocuronium:** Ephedrine may reduce the onset time of neuromuscular blockade when used for intubation with rocuronium if administered simultaneously with anesthetic induction. **Epidural anesthesia:** Ephedrine may decrease the efficacy of epidural blockade by hastening the regression of sensory analgesia.
- **Theophylline:** concomitant use of ephedrine may increase the frequency of nausea, nervousness, and insomnia.
- **Cardiac glycosides:** giving ephedrine with a cardiac glycoside, such as digitalis, may increase the possibility of arrhythmias.

USE IN SPECIFIC POPULATIONS

Pregnancy
Available data from randomized studies, case series, and reports of ephedrine sulfate use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, there are clinical considerations due to underlying conditions.

Untreated hypotension associated with spinal anesthesia for cesarean section is associated with an increase in maternal nausea and vomiting. A decrease in uterine blood flow due to maternal hypotension may result in fetal bradycardia and acidosis.

Cases of potential metabolic acidosis in newborns at delivery with maternal ephedrine exposure have been reported in the literature. These reports describe umbilical artery pH of ≤7.2 at the time of delivery. Monitoring of the newborn for signs and symptoms of metabolic acidosis may be required. Monitoring of infant's acid-base status is warranted to ensure that an episode of acidosis is acute and reversible.

Lactation
A single published case report indicates that ephedrine is present in human milk. However, no information is available on the effects of the drug 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 Ephedrine Sulfate Injection, USP and any potential adverse effects on the breastfed child from Ephedrine Sulfate Injection, USP or from the underlying maternal condition.

Pediatric Use
The safety and effectiveness of Ephedrine Sulfate Injection, USP in pediatric patients have not been established.

Geriatric Use
Clinical studies of ephedrine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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. This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment
Ephedrine and its metabolite are excreted in urine. In patients with renal impairment, excretion of ephedrine is likely to be affected with a corresponding increase in elimination half-life, which will lead to slow elimination of ephedrine and consequently prolonged pharmacological effect and potentially adverse reactions. Monitor patients with renal impairment carefully after the initial bolus dose for adverse events.

DOSAGE AND ADMINISTRATION

Dosage
- Initial, 5 to 10 mg IV bolus; titration, may administer repeat boluses as needed, adjusting to blood pressure goal; MAX total, 50 mg.
- Adjust dosage according to the blood pressure goal (i.e., titrate to effect).

Administration
Ephedrine Sulfate Injection, USP must be diluted before administration as an intravenous bolus to achieve the desired concentration. Dilute with normal saline or 5% dextrose in water.

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For bolus intravenous administration, prepare a solution containing a final concentration of 5 mg/mL of Ephedrine Sulfate Injection, USP:

- Withdraw 50 mg (1 mL of 50 mg/mL) of Ephedrine Sulfate Injection, USP and dilute with 9 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
- Withdraw an appropriate dose of the 5 mg/mL solution prior to bolus intravenous administration.

Storage
Store in original carton at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from light; discard unused portion

OVERDOSAGE

Overdose of ephedrine can cause a rapid rise in blood pressure. In the case of an overdose, careful monitoring of blood pressure is recommended. If blood pressure continues to rise to an unacceptable level, parenteral antihypertensive agents can be administered at the discretion of the clinician.

ENDING INFORMATION

For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**.

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