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Press Release

Hikma responds to COVID-19 shortage with launch of Propofol Injectable Emulsion, USP

Sedative for patients on ventilators currently in short supply in the US

London, 12 May 2020 – Hikma Pharmaceuticals PLC (Hikma, Group), the multinational pharmaceutical company, announces the launch of Propofol Injectable Emulsion, USP, 20 mL, 50 mL and 100 mL Vials, in the United States through its US affiliate, Hikma Pharmaceuticals USA Inc., following approval of its supplemental Abbreviated New Drug Application by the U.S. Food and Drug Administration (FDA).

Propofol Injectable Emulsion is indicated for the initiation and maintenance of sedation and anesthesia, including for intubated, mechanically ventilated adults in the Intensive Care Unit. It is currently on the FDA's Drug Shortage List, following a surge in demand due to the increase in hospitalized, ventilated patients resulting from the COVID-19 pandemic.

In order to get needed supplies to patients as quickly as possible, Hikma is launching with available, limited quantities of its 20 mL and 100 mL vials, with 50 mL vials to follow shortly thereafter. The company is working quickly to scale up manufacturing and will continue releasing product as soon as it is available.

"The launch of Propofol is the latest example of Hikma's ongoing, company-wide commitment to delivering essential medicines to our customers and their patients during this critical time," said Riad Mishlawi, President of Injectables, Hikma. "We have focused our strong US and global manufacturing capabilities on producing medicines that are in highest demand due to the outbreak of COVID-19 including anaesthetics, pain medicines, sedatives, neuromuscular blocking agents, anti-infectives and other support medications. We are grateful to the FDA for their timely approval of our application for Propofol Injection and look forward to delivering this needed medicine to hospitals and patients."

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.

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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 Propofol Injectable Emulsion, USP

CONTRAINDICATIONS

Propofol injectable emulsion is contraindicated in patients with a known hypersensitivity to propofol or any of its components. Propofol injectable emulsion is contraindicated in patients with allergies to eggs, egg products, soybeans or soy products.

WARNINGS & PRECAUTIONS

- Use of propofol has been associated with both fatal and life-threatening anaphylactic and anaphylactoid reactions.
- For general anesthesia or monitored anesthesia care (MAC) sedation, propofol should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.
- For sedation of intubated, mechanically ventilated patients in the Intensive Care Unit (ICU), propofol should be administered only by persons skilled in the management of critically ill patients and trained in cardiovascular resuscitation and airway management.
- **Use of propofol infusions for both adult and pediatric ICU sedation has been associated with a constellation of metabolic derangements and organ system failures, referred to as Propofol Infusion Syndrome, that have resulted in death.**
- Abrupt discontinuation of propofol prior to weaning or for daily evaluation of sedation levels should be avoided.
- Propofol injectable emulsion should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established.
- **There have been reports in which failure to use aseptic technique when handling propofol injectable emulsion was associated with microbial contamination of the product and with fever, infection, sepsis, other life-threatening illness, and death. Do not use if contamination is suspected. Discard unused drug product as directed within the required time limits.**
- **There have been reports, in the literature and other public sources, of the transmission of bloodborne pathogens (such as Hepatitis B, Hepatitis C, and HIV) from unsafe injection practices, and use of propofol vials intended for single use on multiple persons. Propofol injectable emulsion vial is never to be accessed more than once or used on more than one person.**
- Pediatric Neurotoxicity: published animal studies demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for longer than 3 hours.

- A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated, or ASA-PS III or IV patients.
- Propofol use requires caution when administered to patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.
- When propofol is administered to an epileptic patient, there is a risk of seizure during the recovery phase.
- Attention should be paid to minimize pain on administration of propofol. Transient local pain can be minimized if the larger veins of the forearm or antecubital fossa are used.
- Pain during intravenous injection may also be reduced by prior injection of IV lidocaine (1 mL of a 1% solution). it is recommended that lidocaine be administered prior to propofol administration or that it be added to propofol immediately before administration and in quantities not exceeding 20 mg lidocaine/200 mg propofol.
- Perioperative myoclonia, rarely including convulsions and opisthotonos, has occurred in association with propofol administration.
- Clinical features of anaphylaxis, including angioedema, bronchospasm, erythema, and hypotension, occur rarely following propofol administration.
- There have been rare reports of pulmonary edema in temporal relationship to the administration of propofol, although a causal relationship is unknown.
- Rarely, cases of unexplained postoperative pancreatitis (requiring hospital admission) have been reported after anesthesia in which propofol was one of the induction agents used. Due to a variety of confounding factors in these cases, including concomitant medications, a causal relationship to propofol is unclear.
- Propofol has no vagolytic activity. Reports of bradycardia, asystole, and rarely, cardiac arrest have been associated with propofol. Pediatric patients are susceptible to this effect, particularly when fentanyl is given concomitantly. The intravenous administration of anticholinergic agents (e.g., atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (e.g., succinylcholine) or surgical stimuli.
- Intensive Care Unit Sedation: the administration of propofol should be initiated as a continuous infusion and changes in the rate of administration made slowly (greater than 5 min) in order to minimize hypotension and avoid acute overdosage.
- Failure to reduce the infusion rate in patients receiving propofol for extended periods may result in excessively high blood concentrations of the drug. Thus, titration to clinical response and daily evaluation of sedation levels are important during use of propofol infusion for ICU sedation, especially when it is used for long durations.
- Opioids and paralytic agents should be discontinued and respiratory function optimized prior to weaning patients from mechanical ventilation. Infusions of propofol should be adjusted to maintain a light level of sedation prior to weaning patients from mechanical ventilatory support.
- Since propofol injectable emulsion is formulated in an oil-in-water emulsion, elevations in serum triglycerides may occur when propofol is administered for extended periods of time. Administration of propofol should be adjusted if fat is being inadequately cleared from the body.
- The long-term administration of propofol to patients with renal failure and/or hepatic insufficiency has not been evaluated.
- Neurosurgical Anesthesia: when propofol is used in patients with increased intracranial pressure or impaired cerebral circulation, significant decreases in mean arterial pressure should be avoided because of the resultant decreases in cerebral perfusion pressure.
- Cardiac Anesthesia: slower rates of administration should be utilized in premedicated patients, geriatric patients, patients with recent fluid shifts, and patients who are hemodynamically unstable. Fluid deficits should be corrected prior to administration of propofol.

Information for Patients

- Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle, or hazardous machinery or signing legal documents may be impaired for some time after general anesthesia or sedation.
- Studies conducted in young animals and children suggest repeated or prolonged use of general

anesthetic or sedation drugs in children younger than 3 years may have negative effects on their developing brains.

ADVERSE REACTIONS

The following adverse reactions have been reported at incidences greater than 1% probably causally related: Cardiovascular (bradycardia, arrhythmia, tachycardia nodal, hypotension, hypertension, decreased cardiac output), Central Nervous System (movement), Injection Site (burning/stinging or pain), Metabolic/Nutritional (hyperlipemia), Respiratory (apnea, respiratory acidosis during weaning), and Skin and Appendages (rash, pruritus).

The following adverse reactions have been reported at incidences less than 1% probably causally related: Body as a Whole (anaphylaxis/anaphylactoid reaction, perinatal disorder, tachycardia, bigeminy, bradycardia, premature ventricular contractions, hemorrhage, ECG abnormal, arrhythmia atrial fever, extremities pain, anticholinergic syndrome), Cardiovascular (premature atrial contractions, syncope), Central Nervous System (hypertonia/dystonia, paresthesia, agitation), Digestive (hypersalivation, nausea), Hemic/Lymphatic (leukocytosis), Injection Site (phlebitis, pruritus), Metabolic (hypomagnesemia), Musculoskeletal (myalgia), Nervous (dizziness, agitation, chills, somnolence, delirium), Respiratory (wheezing, cough, laryngospasm, hypoxia, decreased lung function), Skin and Appendages (flushing, pruritus), Special Senses (amblyopia, vision abnormal), and Urogenital (cloudy urine, green urine).

The following adverse reactions have been reported at incidences less than 1% causal relationship unknown: Body as a Whole (asthenia, awareness, chest pain, extremities pain, fever, increased drug effect, neck rigidity/stiffness, trunk pain, fever, sepsis, whole body weakness) Cardiovascular (arrhythmia, atrial fibrillation, atrioventricular heart block, bigeminy, bleeding, bundle branch block, cardiac arrest, ECG abnormal, edema, extrasystole, heart block, hypertension, myocardial infarction, myocardial ischemia, premature ventricular contractions, ST segment depression, supraventricular tachycardia, tachycardia, ventricular fibrillation, right heart failure, ventricular tachycardia), Central Nervous System (abnormal dreams, agitation, amorous behavior, anxiety, bucking/jerking/thrashing, chills/shivering/clonic/myoclonic movement, combativeness, confusion, delirium, depression, dizziness, emotional lability, euphoria, fatigue, hallucinations, headache, hypotonia, hysteria, insomnia, moaning, neuropathy, opisthotonos, rigidity, seizures, somnolence, tremor, twitching, intracranial hypertension, thinking abnormal), Digestive (cramping, diarrhea, dry mouth, enlarged parotid, nausea, swallowing, vomiting, ileus, liver function abnormal), Hematologic/Lymphatic (coagulation disorder, leukocytosis), Injection Site (hives/itching, phlebitis, redness/discoloration), Metabolic/Nutritional (hyperkalemia, hyperlipemia, BUN increased, creatinine increased, dehydration, hyperglycemia, metabolic acidosis, osmolality increased), Respiratory (bronchospasm, burning in throat, cough, dyspnea, hiccough, hyperventilation, hypoventilation, hypoxia, laryngospasm, pharyngitis, sneezing, tachypnea, upper airway obstruction), Skin and Appendages (conjunctival hyperemia, diaphoresis, urticaria, rash), Special Senses (diplopia, ear pain, eye pain, nystagmus, taste perversion, tinnitus), and Urogenital (oliguria, urine retention, kidney failure).

DRUG INTERACTIONS

The induction dose requirements of propofol may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (e.g., morphine, meperidine, and fentanyl, etc.) and combinations of opioids and sedatives (e.g., benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic or sedative effects of propofol and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia or sedation, the rate of propofol administration should be adjusted according to the desired level of anesthesia or sedation and may be reduced in the presence of supplemental analgesic agents (e.g., nitrous oxide or opioids). The concurrent administration of potent inhalational agents (e.g., isoflurane, enflurane, and halothane) during maintenance with propofol has not

been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic or sedative and cardiorespiratory effects of propofol.

The concomitant use of valproate and propofol may lead to increased blood levels of propofol. Reduce the dose of propofol when co-administering with valproate. Monitor patients closely for signs of increased sedation or cardiorespiratory depression.

Propofol does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (e.g., succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed in adults. In pediatric patients, administration of fentanyl concomitantly with propofol may result in serious bradycardia.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There are no adequate and well-controlled studies in pregnant women.

Labor and delivery
Propofol is not recommended for obstetrics, including cesarean section deliveries. Propofol crosses the placenta, and as with other general anesthetic agents, the administration of propofol may be associated with neonatal depression.

Nursing mothers
Propofol is not recommended for use in nursing mothers because propofol has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric use
The safety and effectiveness of propofol have been established for induction of anesthesia in pediatric patients aged 3 years and older and for the maintenance of anesthesia aged 2 months and older. Propofol is not recommended for the induction of anesthesia in patients younger than 3 years of age and for the maintenance of anesthesia in patients younger than 2 months of age as safety and effectiveness have not been established. In pediatric patients, administration of fentanyl concomitantly with propofol may result in serious bradycardia.

Propofol is not indicated for use in pediatric patients for ICU sedation or for MAC sedation for surgical, nonsurgical or diagnostic procedures as safety and effectiveness have not been established. There have been anecdotal reports of serious adverse events and death in pediatric patients with upper respiratory tract infections receiving propofol for ICU sedation.

Published juvenile animal studies demonstrate that the administration of anesthetic and sedation drugs, such as propofol, that either block NMDA receptors or potentiate the activity of GABA during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis.

Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Geriatric use

The effect of age on induction dose requirements for propofol was assessed in an open-label study involving 211 unpremedicated patients with approximately 30 patients in each decade between the ages of 16 and 80. The average dose to induce anesthesia was calculated for patients up to 54 years of age and for patients 55 years of age or older. The average dose to induce anesthesia in patients up to 54 years of age was 1.99 mg/kg and in patients above 54 it was 1.66 mg/kg. Subsequent clinical studies have demonstrated lower dosing requirements for subjects greater than 60 years of age.

A lower induction dose and a slower maintenance rate of administration of propofol should be used in elderly patients. In this group of patients, rapid (single or repeated) bolus administration should not be used in order to minimize undesirable cardiorespiratory depression. All dosing should be titrated according to patient condition and response.

DOSAGE AND ADMINISTRATION

Refer to package insert for dosage and administration instructions for induction of general anesthesia, maintenance of anesthesia, and monitored anesthesia care (MAC) sedation. Also refer to package insert for a summary of dosage guidelines table. Dosages and rates of administration in this table should be individualized and titrated to clinical response.

Propofol blood concentrations at steady state are generally proportional to infusion rates, especially in individual patients. Undesirable effects such as cardiorespiratory depression are likely to occur at higher blood concentrations which result from bolus dosing or rapid increases in the infusion rate. An adequate interval (3 minutes to 5 minutes) must be allowed between dose adjustments to allow for and assess the clinical effects.

Shake well before use. Do not use if there is evidence of excessive creaming or aggregation, if large droplets are visible, or if there are other forms of phase separation indicating that the stability of the product has been compromised. Slight creaming, which should disappear after shaking, may be visible upon prolonged standing.

When administering propofol by infusion, syringe or volumetric pumps are recommended to provide controlled infusion rates. When infusing propofol to patients undergoing magnetic resonance imaging, metered control devices may be utilized if mechanical pumps are impractical.

Changes in vital signs indicating a stress response to surgical stimulation or the emergence from anesthesia may be controlled by the administration of 25 mg (2.5 mL) to 50 mg (5 mL) incremental boluses and/or by increasing the infusion rate of propofol.

For minor surgical procedures (e.g., body surface) nitrous oxide (60% to 70%) can be combined with a variable rate propofol infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (e.g., intra-abdominal), or if supplementation with nitrous oxide is not provided, administration rate(s) of propofol and/or opioids should be increased in order to provide adequate anesthesia.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of propofol at rates higher than are clinically necessary. Generally, rates of 50 mcg/kg/min to 100 mcg/kg/min in adults should be achieved during maintenance in order to optimize recovery times.

Other drugs that cause CNS depression (e.g., sedatives, anesthetics, and opioids) can increase CNS depression induced by propofol. Morphine premedication (0.15 mg/kg) with nitrous oxide 67% in oxygen has been shown to decrease the necessary propofol injection maintenance infusion rate and therapeutic blood concentrations when compared to non-narcotic (lorazepam) premedication.

Compatibility and Stability: Propofol injectable emulsion should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: Propofol injectable emulsion is provided as a ready-to-use formulation. However, should dilution be necessary, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic).

Administration with Other Fluids: Compatibility of propofol injectable emulsion with the coadministration of blood/serum/plasma has not been established. When administered using a y-type infusion set, propofol injectable emulsion has been shown to be compatible with the following intravenous fluids.

- 5% Dextrose Injection, USP
- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures
General
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Propofol should only be administered through a filter with a pore size of 5 micron or greater unless it has been demonstrated that the filter does not restrict the flow of propofol and/or cause the breakdown of the emulsion. Filters should be used with caution and where clinically appropriate. Continuous monitoring is necessary due to the potential for restricted flow and/or breakdown of the emulsion.

Do not use if there is evidence of separation of the phases of the emulsion.

Refer to package insert for guidelines for aseptic technique for general anesthesia/MAC sedation and for ICU sedation.

Drug Abuse and Dependence
There are reports of the abuse of propofol for recreational and other improper purposes, which have resulted in fatalities and other injuries. Instances of self-administration of propofol by healthcare professionals have also been reported, which have resulted in fatalities and other injuries. Inventories of propofol should be stored and managed to prevent the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting.

Overdosage
If overdosage occurs, propofol administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids, and administering pressor agents and/or anticholinergic agents.

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 FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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