Press Release

Hikma launches Cisatracurium Besylate Injection, USP in the US

London, 25 March 2025 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Cisatracurium Besylate Injection, USP in 200mg/20mL and 20mg/10mL doses in the US. The product is indicated:

- as an adjunct to general anesthesia to facilitate tracheal intubation in adults and in pediatric patients 1 month to 12 years of age
- to provide skeletal muscle relaxation in adults during surgical procedures or during mechanical ventilation in the ICU
- to provide skeletal muscle relaxation during surgical procedures via infusion in pediatric patients 2 years and older

According to IQVIA, US sales of Cisatracurium Besylate Injection, USP, 200mg/20mL and 20mg/10mL, were approximately $14 million in the 12 months ending January 2025.

Hikma is a top three supplier of generic injectable medicines by volume in the US[1], with a growing portfolio of more than 170 products. We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that enhance patient care.

- ENDS –

This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.

Enquiries

Hikma Pharmaceuticals PLC

Susan Ringdal
EVP, Strategic Planning and Global Affairs
+44 (0)20 7399 2760/ +44 7776 477050

Steven Weiss
US Communications
+1 732 788 8279

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

Hikma helps put better health within reach every day for millions of people around the world. For more than 45 years, we've been creating high-quality medicines and making them accessible to the people who need them.

[1] Source: IQVIA MAT January 2025, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

hikma.

Headquartered in the UK, we are a global company with a local presence across North America, 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 9,500 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 Cisatracurium Besylate Injection, USP, 200mg/20mL and 20mg/10mL:

Please see package insert for referenced section/section numbering, where appropriate.

CONTRAINDICATIONS

- Cisatracurium besylate injection is contraindicated in patients with known hypersensitivity to cisatracurium. Severe anaphylactic reactions to cisatracurium besylate injection have been reported [see *Warnings and Precautions (5.4)].*
- The use of 10 mL cisatracurium besylate injection multiple-dose vials is contraindicated for use in pediatric patients less than 1 month of age and low birth-weight infants because the formulation contains benzyl alcohol *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.4)].*

WARNINGS & PRECAUTIONS

- **Residual Paralysis –** Cisatracurium besylate injection has been associated with residual paralysis. Patients with neuromuscular diseases (e.g., myasthenia gravis and myasthenic syndrome) and carcinomatosis may be at higher risk of residual paralysis.
- **Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative in 10 mL Multiple-Dose Vials –** Serious and fatal adverse reactions including “gasping syndrome” can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including cisatracurium besylate injection.
- **Risk of Seizure –** Laudanosine, an active metabolite of cisatracurium besylate injection, has been shown to cause seizures in animals. Cisatracurium besylate injection-treated patients with renal or hepatic impairment may have higher metabolite concentrations (including laudanosine) than patients with normal renal and hepatic function. Therefore, patients with renal or hepatic impairment receiving extended administration of cisatracurium besylate injection may be at higher risk of seizures.
- **Hypersensitivity Reactions Including Anaphylaxis –** Severe hypersensitivity reactions, including fatal and life-threatening anaphylactic reactions, have been reported.
- **Risk of Death Due to Medication Errors –** Administration of cisatracurium besylate injection results in paralysis, which may lead to respiratory arrest and death, a progression that may be more likely to occur in a patient for whom it is not intended.
- **Risks Due to Inadequate Anesthesia –** Neuromuscular blockade in the conscious patient can lead to distress. Use cisatracurium besylate injection in the presence of appropriate sedation or general anesthesia.
- **Risks for Infection –** The 20 mL vial of cisatracurium besylate injection is intended only for administration as an infusion for use in a single patient in the ICU. The 20 mL vial should not be used multiple times because there is higher risk of infection (the 20 mL vial does not contain a preservative).
- **Potentiation of Neuromuscular Blockade –** Certain drugs may enhance the neuromuscular blocking action of cisatracurium besylate injection including inhalational anesthetics, antibiotics, magnesium salts, lithium, local anesthetics, procainamide and quinidine. Additionally, acid-base and/or serum electrolyte abnormalities may potentiate the action of neuromuscular blocking agents.
- **Resistance to Neuromuscular Blockade with Certain Drugs –** Shorter durations of neuromuscular block may occur and cisatracurium besylate injection infusion rate requirements may be higher in patients chronically administered phenytoin or carbamazepine.
- **Malignant Hyperthermia (MH) –** Cisatracurium besylate injection has not been studied in MH-susceptible patients.

ADVERSE REACTIONS

Clinical Studies Experience
Adverse Reactions in Clinical Trials of Cisatracurium Besylate Injection in Surgical Patients

The data presented in the package insert are based on studies involving 945 surgical patients who received cisatracurium besylate injection in conjunction with other drugs in US and European clinical studies in a variety of procedures. Adverse reactions that occurred at a rate of less than 1% were bradycardia, hypotension, flushing, bronchospasm, and rash.

Adverse Reactions in Clinical Trials of Cisatracurium Besylate Injection in Intensive Care Unit Patients
The adverse reactions presented below were from studies involving 68 adult ICU patients who received cisatracurium besylate injection in conjunction with other drugs in US and European clinical studies. One patient experienced bronchospasm. In one of the two ICU studies, a randomized and double-blind study of ICU patients using TOF neuromuscular monitoring, there were two reports of prolonged recovery (range: 167 and 270 minutes) among 28 patients administered cisatracurium besylate injection and 13 reports of prolonged recovery (range: 90 minutes to 33 hours) among 30 patients administered vecuronium.

Postmarketing Experience
The following events have been identified during post-approval use of cisatracurium besylate injection in conjunction with one or more anesthetic agents in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to cisatracurium besylate injection: anaphylaxis, histamine release, prolonged neuromuscular block, muscle weakness, myopathy.

DRUG INTERACTIONS

Clinically Significant Drug Interactions
Below displays clinically significant drug interactions with cisatracurium besylate injection.

Succinylcholine: The use of succinylcholine prior to cisatracurium besylate injection administration may decrease the time to onset of maximum neuromuscular blockade but has no effect on the duration of neuromuscular blockade.

Inhalational Anesthetics: Administration of inhalational anesthetics with nitrous oxide/oxygen for greater than 30 minutes to achieve 1.25 Minimum Alveolar Concentration (MAC) may prolong the duration of action of initial and maintenance doses of cisatracurium besylate injection. This may potentiate the neuromuscular blockade.

Antibiotics, Local anesthetics, Magnesium salts, Procainamide, Lithium, Quinidine: May prolong the neuromuscular blockade action of cisatracurium besylate injection.

Phenytoin, Carbamazepine: May increase resistance to the neuromuscular blockade action of cisatracurium besylate injection resulting in shorter durations of neuromuscular blockade and infusion rate requirements may be higher.

Drugs Without Clinically Significant Drug Interactions with Cisatracurium Besylate Injection
In clinical studies, propofol had no effect on the duration of action or dosing requirements for cisatracurium besylate injection. Cisatracurium besylate injection is not compatible with propofol for Y-site administration.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
The 10 mL cisatracurium besylate injection multiple-dose vials contain the preservative benzyl alcohol. Therefore, if cisatracurium besylate injection is needed during pregnancy, consider using a benzyl alcohol-free formulation (i.e., 5 mL and 20 mL cisatracurium besylate injection single-dose vials). Because benzyl alcohol is rapidly metabolized by a pregnant woman, benzyl alcohol exposure in the fetus is unlikely. However, adverse reactions have occurred in premature neonates and low birth weight infants who received intravenously administered benzyl alcohol-containing drugs.

Clinical Considerations
Labor or Delivery
The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of preeclampsia or eclampsia of pregnancy.

Lactation
Risk Summary
The 10 mL cisatracurium besylate injection multiple-dose vials contains the preservative benzyl alcohol. Therefore, if cisatracurium besylate injection is needed during lactation, consider using a benzyl alcohol-free formulation (i.e., 5 mL and 20 mL cisatracurium besylate injection single-dose vials). Because benzyl alcohol is rapidly metabolized by a lactating woman, benzyl alcohol exposure in the breastfed infant is unlikely. However, adverse reactions have occurred in premature neonates and low birth weight infants who received intravenously administered benzyl alcohol-containing drugs.

Pediatric Use
The safety and effectiveness of cisatracurium besylate injection as an adjunct to general anesthesia to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery in pediatric patients 1 month through 12 years of age were established from three studies in pediatric patients.

Serious adverse reactions including fatal reactions and the “gasping syndrome” occurred in premature neonates and infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. The use of 10 mL cisatracurium besylate injection multiple-dose vials is contraindicated in pediatric patients less than 1 month of age and low birth-weight infants because these patients are more likely to develop benzyl alcohol toxicity.

Geriatric Use
Because the time to maximum neuromuscular blockade is approximately 1 minute slower in geriatric patients compared to younger patients, consider extending the interval between administering cisatracurium besylate injection and attempting intubation by at least 1 minute to achieve adequate intubation conditions. This difference should also be taken into account when selecting a neuromuscular blocking agent (e.g., the need to rapidly secure the airway) and when initiating laryngoscopy.

Patients with Renal Impairment
The time to 90% neuromuscular blockade was 1 minute slower in patients with end-stage renal disease than in patients with normal renal function. Therefore, consider extending the interval between administering cisatracurium besylate injection and attempting intubation by at least 1 minute to achieve adequate intubation conditions.

Patients with Hepatic Impairment
The pharmacokinetic study analysis in patients with end-stage liver disease undergoing liver transplantation and healthy subjects undergoing elective surgery indicated slightly larger volumes of distribution in liver transplant patients with slightly higher plasma clearances of cisatracurium.

Burn Patients
Patients with burns have been shown to develop resistance to nondepolarizing neuromuscular blocking agents. The extent of altered response depends upon the size of the burn and the time elapsed since the burn injury. Cisatracurium besylate injection has not been studied in patients with burns. However, based on its structural similarity to another neuromuscular blocking agent, consider the possibility of increased dosage requirements and shortened duration of action if cisatracurium besylate injection is administered to burn patients.

Patients with Hemiparesis or Paraparesis
Patients with hemiparesis or paraparesis may demonstrate resistance to nondepolarizing neuromuscular blocking agents in the affected limbs. To avoid inaccurate dosing, perform neuromuscular monitoring on a non-paretic limb.

Patients with Neuromuscular Disease
Profound and prolonged neuromuscular blockade may occur in patients with neuromuscular diseases (e.g., myasthenia gravis and myasthenic syndrome) and carcinomatosis. Therefore, a lower maximum initial bolus is recommended in these patients.

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions
Risk of Medication Errors
Accidental administration of neuromuscular blocking agents may be fatal. Store cisatracurium besylate injection with the cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product.

Important Administration Instructions
- Cisatracurium besylate injection is for intravenous use only.

- Administer cisatracurium besylate injection in carefully adjusted dosage by or under the supervision of experienced clinicians who are familiar with the drug's actions and the possible complications.
- Use cisatracurium besylate injection only if the following are immediately available: personnel and facilities for resuscitation and life support (tracheal intubation, artificial ventilation, oxygen therapy); and an antagonist of cisatracurium besylate injection.
- The dosage information which follows is intended to serve as an initial guide for individual patients; base subsequent cisatracurium besylate injection dosage on the patients' responses to the initial doses.
- Use a peripheral nerve stimulator to:
    - Determine the adequacy of neuromuscular blockade (e.g., need for additional cisatracurium besylate injection doses, reduction of the infusion rate).
    - Minimize risk of overdosage or underdosage.
    - Assess the extent of recovery from neuromuscular blockade (e.g., spontaneous recovery or recovery after administration of a reversal agent, e.g., neostigmine).
    - Appropriately titrate doses to potentially limit exposure to toxic metabolites.
    - Facilitate more rapid reversal of the cisatracurium besylate injection-induced paralysis

Refer to package insert for Recommended Cisatracurium Besylate Injection Dose for Performing Tracheal Intubation, Recommended Maintenance Bolus Cisatracurium Besylate Injection Doses in Adult Surgical Procedures, Dosage in Burn Patients, Dosage for Continuous Infusion, and Rate Tables for Continuous Infusion.

Preparation of Cisatracurium Besylate Injection
Visually inspect cisatracurium besylate injection for particulate matter and discoloration prior to administration. If a cisatracurium besylate injection solution is cloudy or contains visible particulates, do not use cisatracurium besylate injection. Cisatracurium besylate injection is a colorless to slightly yellow or greenish-yellow solution. Discard unused portion of the 5 mL and 20 mL single-dose vials.

Cisatracurium besylate injection may be diluted to 0.1 mg/mL in the following solutions:
- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP, or
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP

Store these diluted cisatracurium besylate injection solutions either in a refrigerator or at room temperature for 24 hours without significant loss of potency.

Cisatracurium besylate injection also may be diluted to 0.1 mg/mL or 0.2 mg/mL in the following solution:
- Lactated Ringer's and 5% Dextrose Injection

Store this diluted cisatracurium besylate injection solution under refrigeration for no more than 24 hours. Do not dilute cisatracurium besylate injection in Lactated Ringer's Injection, USP due to chemical instability.

Drug Compatibility
Cisatracurium besylate injection is compatible and may be administered with the following solutions through Y-site administration:
- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- Sufentanil Citrate Injection, diluted as directed
- Alfentanil Hydrochloride Injection, diluted as directed
- Fentanyl Citrate Injection, diluted as directed
- Midazolam Hydrochloride Injection, diluted as directed
- Droperidol Injection, diluted as directed

Cisatracurium besylate injection is acidic (pH = 3.25 to 3.65) and may not be compatible with alkaline solution having a pH greater than 8.5 (e.g., barbiturate solutions). Therefore, do not administer cisatracurium besylate injection and alkaline solutions simultaneously in the same intravenous line. Cisatracurium besylate injection is not compatible with propofol injection or ketorolac injection for Y-site administration. Compatibility studies with other parenteral products have not been conducted.

hikma.

OVERDOSAGE

Overdosage with neuromuscular blocking agents may result in neuromuscular blockade beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured.

Once recovery from neuromuscular block begins, further recovery may be facilitated by administration of a cholinesterase inhibitor (e.g., neostigmine, edrophonium) in conjunction with an appropriate cholinergic inhibitor. Cholinesterase inhibitors should not be administered when complete neuromuscular blockade is evident or suspected because the reversal of paralysis may not be sufficient to maintain a patent airway and support an appropriate level of spontaneous ventilation.

INDICATIONS AND USAGE

Cisatracurium besylate injection is indicated:

- as an adjunct to general anesthesia to facilitate tracheal intubation in adults and in pediatric patients 1 month to 12 years of age
- to provide skeletal muscle relaxation in adults during surgical procedures or during mechanical ventilation in the ICU
- to provide skeletal muscle relaxation during surgical procedures via infusion in pediatric patients 2 years and older

Limitations of Use
Cisatracurium besylate injection is not recommended for rapid sequence endotracheal intubation due to the time required for its onset of action.

HOW SUPPLIED/STORAGE AND HANDLING

Cisatracurium Besylate Injection, USP is a clear solution supplied as follows:

Multiple-Dose vials:

Strength (mg of cisatracurium)	Containers	Pack Size	NDC#	Preservative
20 mg/10 mL (2 mg/mL)	Multiple-Dose vials	10 vials per carton	0143-9397-10	Contains 0.9% w/v benzyl alcohol *[see Warnings and Precautions (5.2)]*

Single-Dose vials:

Strength (mg of cisatracurium)	Containers	Pack Size	NDC#	Preservative
10 mg/5 mL (2 mg/mL)	Single-Dose vial	1 vial per carton	0143-9396-01	Does not contain benzyl alcohol
200 mg/20 mL (10 mg/mL)	Single-Dose vials	10 vials per carton	0143-9160-10	Does not contain benzyl alcohol

Discard unused portion of the 5 mL and 20 mL single-dose vials.

Storage
Refrigerate Cisatracurium Besylate Injection, USP at 2°C to 8°C (36°F to 46°F) in the carton to preserve potency. Protect from light. DO NOT FREEZE. Upon removal of the unused vial from refrigeration to room temperature storage conditions (25°C/77°F), use Cisatracurium Besylate Injection, USP within 21 days, even if re-refrigerated.

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
For additional information, please refer to the Multiple-Dose vials Package Insert and the Single-Dose vials

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.

Manufactured by:
HIKMA FARMACEUTICA (PORTUGAL), S.A.
Estrada do Rio da Mo, 8, 8A e 8B – Fervenca – 2705-906 Terrugem SNT, PORTUGAL

Distributed by:
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922 USA

Document Identification Number: HK-3246-v1