ANNEXURE IB

1.4.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCT CHARACTERISTICS)

1	**NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:**
	Product Name: **Proprietary Name:** CISATRA **Generic Name or International Non-Proprietary Name (INN):** Cisatracurium Besylate Injection USP
1.1	**Strength :** 2mg/mL
1.2	**Pharmaceutical Form:** Injection
2	**QUALITATIVE AND QUANTITATIVE COMPOSITIONS:**
2.1	**Qualitative Declaration:** Active component INN Name: Cisatracurium Besylate
2.2	**Quantitative Declaration:** Each mL contains: Cisatracurium Besylate USP Equivalent to Cisatracurium …….. 2 mg Benzyl Alcohol USP-NF.....0.90%v/v (as preservative) Water for Injection USP.....Q.S. USP: United States Pharmacopoeia **For full list of excipients, see section 6.1**
3	**PHARMACEUTICAL FORM:** Injection Clear colourless liquid.

4	**CLINICAL PARTICULARS:**
4.1	**Therapeutic Indications:** Cisatracurium Besylate Injection USP is an intermediate-onset/intermediate-duration neuromuscular blocking agent indicated for inpatients and outpatients as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation in the ICU.
4.2	**Posology and Method of Administration** **Posology:** Route of administration: Intravenous Injection or Infusion The dosage information provided below is intended as a guide only. Doses of Cisatracurium Besylate Injection USP should be individualized. The use of a peripheral nerve stimulator will permit the most advantageous use of Cisatracurium Besylate Injection USP, minimize the possibility of over dosage or under dosage, and assist in the evaluation of recovery. **Adults** **Initial Doses** One of two intubating doses of Cisatracurium Besylate Injection USP may be chosen, based on the desired time to tracheal intubation and the anticipated length of surgery. In addition to the dose of neuromuscular blocking agent, the presence of co-induction agents (e.g., fentanyl and midazolam) and the depth of anesthesia are factors that can influence intubation conditions. Doses of 0.15 (3×ED95) and 0.20 (4×ED95) mg/kg Cisatracurium Besylate Injection USP, as components of a propofol/nitrous oxide/oxygen induction-intubation technique, may produce generally good or excellent conditions for intubation in 2.0 and 1.5 minutes, respectively. Similar intubation conditions may be expected when these doses of Cisatracurium Besylate Injection USP are administered as components of a thiopental/nitrous oxide/oxygen induction-intubation technique. In two intubation studies using thiopental or propofol and midazolam and fentanyl as coinduction agents, excellent intubation conditions were most frequently achieved with the 0.2 mg/kg compared to 0.15 mg/kg dose of cisatracurium. The clinically effective durations of action for 0.15 and 0.20 mg/kg Cisatracurium Besylate Injection USP during propofol anesthesia are 55 minutes (range: 44 to 74 minutes) and 61 minutes (range: 41 to 81 minutes), respectively. Lower doses may result in a longer time for the development of satisfactory intubation conditions.

Doses up to 8 × ED95Cisatracurium Besylate Injection USP have been safely administered to healthy adult patients and patients with serious cardiovascular disease. These larger doses are associated with longer clinically effective durations of action.

Because slower times to onset of complete neuromuscular block were observed in elderly patients and patients with renal dysfunction, extending the interval between administration of Cisatracurium Besylate Injection USP and the intubation attempt for these patients may be required to achieve adequate intubation conditions.

A dose of 0.03 mg/kg Cisatracurium Besylate Injection USP is recommended for maintenance of neuromuscular block during prolonged surgical procedures. Maintenance doses of 0.03 mg/kg each sustain neuromuscular block for approximately 20 minutes. Maintenance dosing is generally required 40 to 50 minutes following an initial dose of 0.15 mg/kg Cisatracurium Besylate Injection USP and 50 to 60 minutes following an initial dose of 0.20 mg/kg Cisatracurium Besylate Injection USP, but the need for maintenance doses should be determined by clinical criteria. For shorter or longer durations of action, smaller or larger maintenance doses may be administered.

Isoflurane or enflurane administered with nitrous oxide/oxygen to achieve 1.25 MAC (Minimum Alveolar Concentration) may prolong the clinically effective duration of action of initial and maintenance doses. The magnitude of these effects may depend on the duration of administration of the volatile agents. Fifteen to 30 minutes of exposure to 1.25 MAC isoflurane or enflurane had minimal effects on the duration of action of initial doses of Cisatracurium Besylate Injection USP and therefore, no adjustment to the initial dose should be necessary when Cisatracurium Besylate Injection USP is administered shortly after initiation of volatile agents. In long surgical procedures during enflurane or isoflurane anesthesia, less frequent maintenance dosing or lower maintenance doses of Cisatracurium Besylate Injection USP may be necessary. No adjustments to the initial dose of Cisatracurium Besylate Injection USP are required when used in patients receiving propofol anesthesia.

Children

Initial Doses

The recommended dose of Cisatracurium Besylate Injection USP for children 2 to 12 years of age is 0.10-0.15 mg/kg administered over 5 to 10 seconds during either halothane or opioid anesthesia. When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.10 mg/kg Cisatracurium Besylate Injection USP produces maximum

neuromuscular block in an average of 2.8 minutes (range: 1.8 to 6.7 minutes) and clinically effective block for 28 minutes (range: 21 to 38 minutes). When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.15 mg/kg Cisatracurium Besylate Injection USP produces maximum neuromuscular block in about 3.0 minutes (range: 1.5 to 8.0 minutes) and clinically effective block (time to 25% recovery) for 36 minutes (range: 29 to 46 minutes).

Infants

Initial Doses

The recommended dose of Cisatracurium Besylate Injection USP for intubation of infants 1 month to 23 months is 0.15 mg/kg administered over 5 to 10 seconds during either halothane or opioid anesthesia. When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.15 mg/kg Cisatracurium Besylate Injection USP produces maximum neuromuscular block in about 2.0 minutes (range: 1.3 to 3.4 minutes) and clinically effective block (time to 25% recovery) for about 43 minutes (range: 34 to 58 minutes).

Use by Continuous Infusion

Infusion in the Operating Room (OR)

After administration of an initial bolus dose of Cisatracurium Besylate Injection USP, a diluted solution of Cisatracurium Besylate Injection USP can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular block during extended surgical procedures. Infusion of Cisatracurium Besylate Injection USP should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation. Accurate dosing is best achieved using a precision infusion device.

Infusion of Cisatracurium Besylate Injection USP should be initiated only after early evidence of spontaneous recovery from the initial bolus dose. An initial infusion rate of 3 mcg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 1 to 2 mcg/kg/min should be adequate to maintain continuous neuromuscular block in the range of 89% to 99% in most pediatric and adult patients under opioid/nitrous oxide/oxygen anesthesia.

Reduction of the infusion rate by up to 30% to 40% should be considered when Cisatracurium Besylate Injection USP is administered during stable isoflurane or enflurane

anesthesia (administered with nitrous oxide/oxygen at the 1.25 MAC level). Greater reductions in the infusion rate of Cisatracurium Besylate Injection USP may be required with longer durations of administration of isoflurane or enflurane.

The rate of infusion of atracurium required to maintain adequate surgical relaxation in patients undergoing coronary artery bypass surgery with induced hypothermia (25°to 28°C) is approximately half the rate required during normothermia. Based on the structural similarity between Cisatracurium Besylate Injection USP and atracurium, a similar effect on the infusion rate of Cisatracurium Besylate Injection USP may be expected.

Spontaneous recovery from neuromuscular block following discontinuation of infusion of Cisatracurium Besylate Injection USP may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

Infusion in the Intensive Care Unit (ICU)

The principles for infusion of Cisatracurium Besylate Injection USP in the OR are also applicable to use in the ICU. An infusion rate of approximately 3 mcg/kg/min (range: 0.5 to 10.2 mcg/kg/min) should provide adequate neuromuscular block in adult patients in the ICU. There may be wide interpatient variability in dosage requirements and these may increase or decrease with time (see PRECAUTIONS - Long-Term Use in the Intensive Care Unit [ICU]). Following recovery from neuromuscular block, readministration of a bolus dose may be necessary to quickly re-establish neuromuscular block prior to reinstitution of the infusion.

Infusion Rate Tables

The amount of infusion solution required per minute will depend upon the concentration of Cisatracurium Besylate Injection USP in the infusion solution, the desired dose of Cisatracurium Besylate Injection USP, and the patient's weight. The contribution of the infusion solution to the fluid requirements of the patient also must be considered. Table 1and Table 2provide guidelines for delivery in mL/hr (equivalent to microdrops/min when 60 microdrops = 1 mL) of Cisatracurium Besylate solutions in concentrations of 0.1 mg/mL (10 mg/100 mL) or 0.4 mg/mL (40 mg/100 mL).

Table 1. Infusion Rates of Cisatracurium Besylate Injection USP for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using Cisatracurium Besylate at a Concentration of 0.1 mg/mL

Patient Weight (kg)	Delivery Rate (mcg/kg/min)				
	1.0	1.5	2.0	3.0	5.0
	Infusion Delivery Rate (mL/hr)				
10	6	9	12	18	30
45	27	41	54	81	135
70	42	63	84	126	210
100	60	90	120	180	300

Table 2. Infusion Rates of Cisatracurium Besylate Injection USP for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using Cisatracurium Besylate at a Concentration of 0.4 mg/mL

Patient Weight (kg)	Delivery Rate (mcg/kg/min)				
	1.0	1.5	2.0	3.0	5.0
	Infusion Delivery Rate (mL/hr)				
10	1.5	2.3	3.0	4.5	7.5
45	6.8	10.1	13.5	20.3	33.8
70	10.5	15.8	21.0	31.5	52.5
100	15.0	22.5	30.0	45.0	75.0

4.3 **Method of administration:** Intravenous Injection or Infusion

4.4 **Contra-indications:**

Cisatracurium Besylate Injection USP is contraindicated in patients with known hypersensitivity to the product and its components.
The 10 mL multiple-dose vial of Cisatracurium Besylate Injection USP is contraindicated for use in premature infants because the formulation contains benzyl alcohol.

4.5 **Special warning and precautions for use:**

Cisatracurium Besylate Injection USP should be administered in carefully adjusted dosage by or under the supervision of experienced clinicians who are familiar with the drug's actions and the possible complications of its use. The drug should not be administered unless personnel and facilities for resuscitation and life support (tracheal intubation, artificial ventilation, oxygen therapy), and an antagonist of Cisatracurium Besylate are immediately available. It is recommended that a peripheral nerve stimulator be used to measure neuromuscular function during the administration of Cisatracurium Besylate in order to monitor drug effect, determine the need for additional doses, and confirm recovery from neuromuscular block.

Cisatracurium Besylate Injection USP has no known effect on consciousness, pain

threshold, thinking, or memory. To avoid distress to the patient, neuromuscular block should not be induced before unconsciousness.

Anaphylaxis

Severe anaphylactic reactions to neuromuscular blocking agents, including Cisatracurium Besylate Injection, have been reported. These reactions have in some cases been life-threatening and fatal. Due to the potential severity of these reactions, the necessary precautions, such as immediate availability of appropriate emergency treatment, should be taken. Precautions should also be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents since cross-reactivity between neuromuscular blocking agents, both depolarizing and non-depolarizing, has been reported in this class of drugs.

Cisatracurium Besylate Injection USP is acidic and may not be compatible with alkaline solutions having a pH greater than 8.5 (e.g., barbiturate solutions).

The multiple-dose vials of Cisatracurium Besylate Injection USP contain benzyl alcohol, which is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administration. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources. Single-use vials (5 mL) of Cisatracurium Besylate Injection USP do not contain benzyl alcohol.

PRECAUTIONS

Because of its intermediate onset of action, Cisatracurium Besylate Injection USP is not recommended for rapid sequence endotracheal intubation.

Recommended doses of Cisatracurium Besylate Injection USP have no clinically significant effects on heart rate; therefore, Cisatracurium Besylate Injection USP will not

counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (e.g., myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (e.g., carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.02 mg/kg Cisatracurium Besylate Injection USP is recommended to assess the level of neuromuscular block and to monitor dosage requirements.

Patients with burns have been shown to develop resistance to nondepolarizing neuromuscular blocking agents, including atracurium. The extent of altered response depends upon the size of the burn and the time elapsed since the burn injury. Cisatracurium Besylate Injection USP has not been studied in patients with burns; however, based on its structural similarity to atracurium, the possibility of increased dosing requirements and shortened duration of action must be considered if Cisatracurium Besylate Injection USP is administered to burn patients.

Patients with hemiparesis or paraparesis also may demonstrate resistance to nondepolarizing muscle relaxants in the affected limbs. To avoid inaccurate dosing, neuromuscular monitoring should be performed on a non-paretic limb.

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. No data are available to support the use of Cisatracurium Besylate Injection USP by intramuscular injection.

Allergic Reactions

Since allergic cross-reactivity has been reported in this class, request information from your patients about previous anaphylactic reactions to other neuromuscular blocking agents.

Renal and Hepatic Disease

No clinically significant alterations in the recovery profile were observed in patients with renal dysfunction or in patients with end-stage liver disease following a 0.1 mg/kg dose of cisatracurium. The onset time was approximately 1 minute faster in patients with end-stage liver disease and approximately 1 minute slower in patients with renal dysfunction than in healthy adult control patients.

Malignant Hyperthermia (MH)

Cisatracurium Besylate Injection USP has not been studied in MH-susceptible patients.

	Because MH can develop in the absence of established triggering agents to recognize and treat MH in any patient undergoing general anesthesia. **Long-Term Use in the ICU** Whenever the use of cisatracurium besylate or any other neuromuscular blocking agent in the ICU is contemplated, it is recommended that neuromuscular function be monitored during administration with a nerve stimulator. Additional doses of cisatracurium besylate or any other neuromuscular blocking agent should not be given before there is a definite response to nerve stimulation. If no response is elicited, infusion administration should be discontinued until a response returns. The effects of hemofiltration, hemodialysis, and hemoperfusion on plasma levels of Cisatracurium Besylate Injection USP and its metabolites are unknown.
4.6	**Paediatric Population** The recommended dose of Cisatracurium Besylate Injection USP for intubation of infants 1 month to 23 months is 0.15 mg/kg administered over 5 to 10 seconds during either halothane or opioid anesthesia. When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.15 mg/kg Cisatracurium Besylate Injection USP produces maximum neuromuscular block in about 2.0 minutes (range: 1.3 to 3.4 minutes) and clinically effective block (time to 25% recovery) for about 43 minutes (range: 34 to 58 minutes).
4.7	**Interaction with other drugs, other forms of interactions:** Cisatracurium Besylate Injection USP has been used safely following varying degrees of recovery from succinylcholine-induced neuromuscular block. Administration of 0.1 mg/kg (2 × ED95) Cisatracurium Besylate Injection USP at 10% or 95% recovery following an intubating dose of succinylcholine (1 mg/kg) produced ≥ 95% neuromuscular block. Prior administration of succinylcholine had no effect on the duration of neuromuscular block following initial or maintenance bolus doses of Cisatracurium Besylate Injection USP. Infusion requirements of Cisatracurium Besylate Injection in patients administered succinylcholine prior to infusions of Cisatracurium Besylate Injection were comparable to or slightly greater than when succinylcholine was not administered. The use of Cisatracurium Besylate Injection before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied. No drug interactions were observed when vecuronium, pancuronium, or atracurium were administered following varying degrees of recovery from single doses or infusions of

	Cisatracurium Besylate Injection USP. Isoflurane or enflurane administered with nitrous oxide/oxygen to achieve 1.25 MAC [Minimum Alveolar Concentration] may prolong the clinically effective duration of action of initial and maintenance doses of Cisatracurium Besylate Injection USP and decrease the required infusion rate of Cisatracurium Besylate Injection USP.The magnitude of these effects may depend on the duration of administration of the volatile agents. Fifteen to 30 minutes of exposure to 1.25 MAC isoflurane or enflurane had minimal effects on the duration of action of initial doses of Cisatracurium Besylate Injection USP and therefore, no adjustment to the initial dose should be necessary when Cisatracurium Besylate Injection USP is administered shortly after initiation of volatile agents. In long surgical procedures during enflurane or isoflurane anesthesia, less frequent maintenance dosing, lower maintenance doses, or reduced infusion rates of Cisatracurium Besylate Injection USP may be necessary. The average infusion rate requirement may be decreased by as much as 30% to 40%. Propofol had no effect on the duration of action or dosing requirements for Cisatracurium Besylate Injection USP. Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Cisatracurium Besylate Injection USP include certain antibiotics (e.g., aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistemethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. Resistance to the neuromuscular blocking action of nondepolarizing neuromuscular blocking agents has been demonstrated in patients chronically administered phenytoin or carbamazepine. While the effects of chronic phenytoin or carbamazepine therapy on the action of cisatracurium besylate are unknown, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher.
4.8	**Additional Information on special population** Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (e.g., myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (e.g., carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.02 mg/kg Cisatracurium Besylate Injection USP is recommended to assess the level of

	neuromuscular block and to monitor dosage requirements. Patients with burns have been shown to develop resistance to nondepolarizing neuromuscular blocking agents, including atracurium. The extent of altered response depends upon the size of the burn and the time elapsed since the burn injury. Patients with hemiparesis or paraparesis also may demonstrate resistance to nondepolarizing muscle relaxants in the affected limbs. To avoid inaccurate dosing, neuromuscular monitoring should be performed on a non-paretic limb. Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. No data are available to support the use of Cisatracurium Besylate Injection USP by intramuscular injection. Patients with renal or hepatic disease, renal dysfunction or in patients with end-stage liver disease, should be taken care . Cisatracurium has not been studied in patients with a history of malignant hyperthermia(MH). Because MH can develop in the absence of established triggering agents, to recognize and treat MH in any patient undergoing general anaesthesia. Whenever the use of cisatracurium besylate or any other neuromuscular blocking agent in the ICU is contemplated, it is recommended that neuromuscular function be monitored during administration with a nerve stimulator. Additional doses of cisatracurium besylate or any other neuromuscular blocking agent should not be given before there is a definite response to nerve stimulation **Geriatrics use** No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between elderly and younger subjects, but greater sensitivity of some older individuals to Cisatracurium Besylate Injection USP cannot be ruled out. Minor differences in the pharmacokinetics of cisatracurium between elderly and young adult patients are not associated with clinically significant differences in the recovery profile of Cisatracurium Besylate Injection USP following a single 0.1 mg/kg dose; the time to maximum block is approximately 1 minute slower in elderly patients.
4.9	**Paediatric Population** Cisatracurium Besylate Injection USP has not been studied in pediatric patients below the

	age of 1 month. The recommended dose of Cisatracurium Besylate Injection USP for intubation of infants 1 month to 23 months is 0.15 mg/kg administered over 5 to 10 seconds during either halothane or opioid anesthesia. When administered during stable opioid/nitrous oxide/oxygen, 0.15 mg/kg Cisatracurium Besylate Injection USP produces maximum neuromuscular block in about 2.0 minutes (range: 1.3 to 3.4 minutes) and clinically effective block (time to 25% recovery) for about 43 minutes (range: 34 to 58 minutes).
4.10	**Fertility, Pregnancy & Lactation:** **Pregnant Women** There are no adequate and well-controlled studies of Cisatracurium Besylate Injection USP in pregnant women. Because animal studies are not always predictive of human response, Cisatracurium Besylate Injection should be used during pregnancy only if clearly needed. **Labour and Delivery** anesthesia The use of Cisatracurium Besylate Injection USP during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether Cisatracurium Besylate administered to the mother has effects on the fetus. **Lactating Women** It is not known whether cisatracurium besylate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following administration of Cisatracurium Besylate Injection USP to a nursing woman **Pediatric use** Cisatracurium Besylate Injection USP has not been studied in pediatric patients below the age of 1 month.
4.11	**Effects on ability to drive and use machines** This precaution is not relevant to the use of cisatracurium. Cisatracurium will always be used in combination with a general anaesthetic and therefore the usual precautions relating to performance of tasks following general anaesthesia apply.
4.12	**Undesirable effects:** The following adverse effects have a possible causal relationship to Cisatracurium Besylate Injection USP (incidence less than 1%): Cardiovascular System: Flushing (0.2%), hypotension (0.2%), and bradycardia (0.4%). Respiratory System: Bronchospasm (0.2%). Dermatological: Rash (0.1%).

	Observed During Clinical Practice In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of cisatracurium besylate 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. **General** Histamine release, hypersensitivity reactions including anaphylactic or anaphylactoid reactions which in some cases have been life threatening and fatal. There are rare reports of wheezing, laryngospasm, bronchospasm, rash and itching following administration of cisatracurium besylate in children. These reported adverse events were not serious and their etiology could not be established with certainty. Musculoskeletal Prolonged neuromuscular block, inadequate neuromuscular block, muscle weakness, and myopathy.
4.13	**Overdose:** Overdosage with neuromuscular blocking agents may result in neuromuscular block 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 an anticholinesterase agent (e.g., neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent. **Antagonism of Neuromuscular Block** Antagonists (such as neostigmine and edrophonium) should not be administered when complete neuromuscular block is evident or suspected. The use of a peripheral nerve stimulator to evaluate recovery and antagonism of neuromuscular block is recommended.
5	**PHARMACOLOGICAL PROPERTIES:**
5.1	**Pharmacodynamic Properties:** **Pharmacotherapeutic Group :** Non-depolarizing Neuromuscular blocking agent ATC code: M03AC11

	The neuromuscular blocking potency of cisatracurium besylate is approximately threefold that of atracurium besylate. The time to maximum block is up to 2 minutes longer for equipotent doses of cisatracurium besylate compared to atracurium besylate. The clinically effective duration of action and rate of spontaneous recovery from equipotent doses of cisatracurium besylate and atracurium besylate are similar. The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of cisatracurium is 0.05 mg/kg (range: 0.048 to 0.053) in adults receiving opioid/nitrous oxide/oxygen anesthesia. For comparison, the average ED_{95} for atracurium when also expressed as the parent bis-cation is 0.17 mg/kg under similar anesthetic conditions.
5.2	**Pharmacokinetic Property:** **General** The neuromuscular blocking activity of cisatracurium besylate is due to parent drug. Cisatracurium plasma concentration-time data following IV bolus administration are best described by a two-compartment open model (with elimination from both compartments) with an elimination half-life ($t_{½}\beta$) of 22 minutes, a plasma clearance (CL) of 4.57 mL/min/kg, and a volume of distribution at steady state (V_{ss}) of 145 mL/kg. Cisatracurium undergoes organ-independent Hofmann elimination (a chemical process dependent on pH and temperature) to form the monoquaternary acrylate metabolite and laudanosine, neither of which has any neuromuscular blocking activity. Following administration of radiolabeled cisatracurium, 95% of the dose was recovered in the urine; less than 10% of the dose was excreted as unchanged parent drug. Laudanosine, a metabolite of cisatracurium (and atracurium) has been noted to cause transient hypotension and, in higher doses, cerebral excitatory effects when administered to several animal species. The relationship between CNS excitation and laudanosine concentrations in humans has not been established. Because cisatracurium is three times more potent than atracurium and lower doses are required, the corresponding laudanosine concentrations following cisatracurium are one third of those that would be expected following an equipotent dose of atracurium. **Distribution** The volume of distribution of cisatracurium is limited by its large molecular weight and high polarity. The $V_{ss}$was equal to 145 mL/kg in healthy 19- to 64-year-old surgical patients receiving opioid anesthesia. The V_{ss} was 21% larger in similar patients receiving

inhalation anesthesia.

Protein Binding

The binding of cisatracurium to plasma proteins has not been successfully studied due to its rapid degradation at physiologic pH. Inhibition of degradation requires nonphysiological conditions of temperature and pH which are associated with changes in protein binding.

Metabolism

The degradation of cisatracurium is largely independent of liver metabolism. Results from in vitro experiments suggest that cisatracurium undergoes Hofmann elimination (a pH and temperature-dependent chemical process) to form laudanosine and the monoquaternary acrylate metabolite. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol (MQA) metabolite. The MQA metabolite can also undergo Hofmann elimination but at a much slower rate than cisatracurium. Laudanosine is further metabolized to desmethyl metabolites which are conjugated with glucuronic acid and excreted in the urine.

Organ-independent Hofmann elimination is the predominant pathway for the elimination of cisatracurium. The liver and kidney play a minor role in the elimination of cisatracurium but are primary pathways for the elimination of metabolites. Therefore, the $t_{½\beta}$ values of metabolites (including laudanosine) are longer in patients with kidney or liver dysfunction and metabolite concentrations may be higher after long-term administration. Most importantly, C_{max} values of laudanosine are significantly lower in healthy surgical patients receiving infusions of cisatracurium besylate than in patients receiving infusions of atracurium (mean ± SD C_{max}: 60 ± 52 and 342 ± 93 ng/mL, respectively).

Elimination

Mean CL values for cisatracurium ranged from 4.5 to 5.7 mL/min/kg in studies of healthy surgical patients. Compartmental pharmacokinetic modeling suggests that approximately 80% of the CL is accounted for by Hofmann elimination and the remaining 20% by renal and hepatic elimination. These findings are consistent with the low magnitude of interpatient variability in CL (16%) estimated as part of the population PK/PD analyses and with the recovery of parent and metabolites in urine. Following C-cisatracurium administration to 6 healthy male patients, 95% of the dose was recovered in the urine (mostly as conjugated metabolites) and 4% in the feces; less than 10% of the dose was excreted as unchanged parent drug in the urine. In 12 healthy surgical patients receiving

	non-radiolabeled cisatracurium who had Foley catheters placed for surgical management, approximately 15% of the dose was excreted unchanged in the urine. In studies of healthy surgical patients, mean $t_{½\beta}$ values of cisatracurium ranged from 22 to 29 minutes and were consistent with the $t_{½\beta}$ of cisatracurium in vitro (29 minutes). The mean ± SD $t_{½\beta}$ values of laudanosine were 3.1 ± 0.4 and 3.3 ± 2.1 hours in healthy surgical patients receiving cisatracurium besylate (n = 10) or atracurium (n = 10), respectively. During IV infusions of cisatracurium besylate, peak plasma concentrations (C_{max}) of laudanosine and the MQA metabolite are approximately 6% and 11% of the parent compound, respectively.
5.3	**Pre-clinical Safety Data** **Animal Pharmacology** The overall neuromuscular blocking profile of cisatracurium in anesthetized cats, dogs and monkeys is very similar to the neuromuscular blocking profile of atracurium. Spontaneous recovery times from neuromuscular blockade produced by single intravenous bolus injections or infusions were independent of both the administered dose and the duration of blockade, and indicated that cisatracurium was devoid of cumulative effects on the neuromuscular junction. High multiples of the ED95 (the effective dose required to produce 95% suppression of the adductor polices muscle twitch response to ulnar nerve stimulation) neuromuscular blocking dose did not produce a correspondingly long duration of action. Like other non-depolarizing neuromuscular blocking agents (e.g., atracurium, vecuronium, mivacurium, doxacurium, d-tubocurarine), the in vivo and in vitro effects of cisatracurium on the neuromuscular junction were reversed by the acetylcholinesterase inhibitor neostigmine. Bolus intravenous administration of cisatracurium besylate at doses that produced clinically useful levels of neuromuscular blockade had no effects on sympathetic efferent pathways and had no vagolytic action. There was at least a fifteen-fold separation between the ED_{95} neuromuscular blocking dose and doses that produced transient inhibition of the autonomic nervous system. The cardiovascular effects of cisatracurium in cats, dogs, and monkeys, at doses that produced complete neuromuscular paralysis, were minimal. Cumulative doses of cisatracurium equivalent to approximately 10 times the ED_{95} decreased mean arterial blood pressure 15 to 20% and had smaller effects on heart rate, cardiac index, total peripheral resistance and left ventricular dP/dt (the change in pressure over the change in time) in

anesthetized dogs. Doses of cisatracurium greater than 10 times the ED_{95} produced significantly smaller cardiovascular effects than approximately equal doses of atracurium in anesthetized dogs. In anesthetized cats, cisatracurium, unlike atracurium, did not increase plasma histamine concentrations and did not produce histamine-like cardiovascular effects at high multiples of the E0115 neuromuscular blocking dose. Doses of cisatracurium equivalent to 20 to 25 times the ED_{95} neuromuscular blocking dose had minimal (<10%) effects on arterial blood pressure and heart rate in nitrous oxide: oxygen and halothane anesthetized rhesus and cynomolgus monkeys. Significantly, no histamine-like cardiovascular effects were observed after bolus intravenous administration of doses as high as 20 to 25 times the estimated ED_{95} neuromuscular blocking dose in monkeys.

Animal Toxicology

Carcinogenesis and fertility studies have not been performed. Cisatracurium besylate was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, a rat bone marrow cytogenetic assay, and an in vitro human lymphocyte cytogenetics assay. As was the case with atracurium, the mouse lymphoma assay was positive both in the presence and absence of exogenous metabolic activation (rat liver S-9). In the absence of S-9, cisatracurium besylate was positive at in vitro cisatracurium concentrations of 40 mcg/mL and higher. The highest non-mutagenic concentration (30 mcg/mL) and incubation time (4 hours) resulted in an AUC approximately 120 times that noted in clinical studies and approximately 8.5 times the mean peak clinical concentration noted. In the presence of S-9, cisatracurium besylate was positive at a cisatracurium concentration of 300 mcg/mL but not at lower or higher concentrations.

Teratology testing in nonventilated pregnant rats treated subcutaneously with maximum subparalyzing doses (4 mg/kg daily; equivalent to 8 × the human ED95 following a bolus dose of 0.2 mg/kg IV) and in ventilated rats treated intravenously with paralyzing doses of cisatracurium besylate at 0.5 and 1.0 mg/kg; equivalent to 10 × and 20 × the human ED95 dose, respectively, revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of Cisatracurium Besylate Injection USP in pregnant women. Because animal studies are not always predictive of human response, Cisatracurium Besylate Injection USP should be used during pregnancy only if clearly needed.

	Doses of 0.2 or 0.4 mg/kg cisatracurium given to female beagles undergoing cesarean section resulted in negligible levels of cisatracurium in umbilical vessel blood of neonates and no deleterious effects on the puppies. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxaemia of pregnancy.
6	**PHARMACEUTICALS PARTICULARS:**
6.1	**List of Excipients:** Benzene Sulphonic Acid IH Benzyl Alcohol USP-NF Water for Injection USP
6.2	**Incompatibilities:** Cisatracurium Besylate Injection USP is acidic and may not be compatible with alkaline solution having a pH greater than 8.5 (e.g., barbiturate solutions). Cisatracurium Besylate Injection USP is not compatible with propofol Injection or ketorolac Injection for Y-site administration. Studies of other parenteral products have not been conducted.
6.3	**Shelf Life:** 24 Months
6.4	**Special Precaution for Storage:** Store in a refrigerator (2°C to 8°C), protected from freezing and light. Upon removal from refrigeration to room temperature, use within 21 days even if re-refrigerated. Keep out of the reach and sight of children.
6.5	**Nature and Contents of Container:** **CISATRA 10ml**(Cisatracurium Besylate Injection USP 2mg/ml) is filled in 10 mL USP Type I amber glass vial plugged with 13mm Bromo butyl rubber plug and sealed with 13mm green colour flip off seal. 1 such vial packed in a carton along with pack insert.

6.6	**Special Precautions for Disposal and other handling:** Cisatracurium Besylate Injection USP diluted in 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; or 5% Dextrose and 0.9% Sodium Chloride Injection, USP to 0.1 mg/mL may be stored either under refrigeration or at room temperature for 24 hours without significant loss of potency. Dilutions to 0.1 mg/mL or 0.2 mg/mL in 5% Dextrose and Lactated Ringer's Injection may be stored under refrigeration for 24 hours. Cisatracurium Besylate Injection USP should not be diluted in Lactated Ringer's Injection, USP due to chemical instability. NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are not clear, or contain visible particulates, should not be used.
7	**MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESS:** **Marketing Authorization Holder:** **Themis Medicare Limited** Address : 11/12 , Udyog Nagar, S.V. Road, Goregaon (West), Mumbai- 400104 Country : India Telephone : 91-22-67607080 E-Mail : themis@themismedicare.com **Manufacturing Site Address:** **Themis Medicare Limited** Address : Sector 6 A, Plot No. 16,17&18 IIE SIDCUL, HARIDWAR-249 403, Uttarakhand. Country : India Telephone : 91-1334-239322/21 E-Mail : hwdqualityhead@themismedicare.com
8	**MARKETING AUTHORIZATION NUMBER:** Not Applicable
9	**DATE OF FIRST REGISTRATION / RENEWAL OF THE REGISTRATION:** Not Applicable
10	**DATE OF REVISION OF THE TEXT:** 04-09-2024
11	**DOSIMETRY (IF APPLICABLE):** Not Applicable
12	**INSTRUCTION FOR PREPARATIONS OF RADIOPHARMACEUTICAL (IF APPLICABLE):** Not Applicable