1.3.1 SUMMARY PRODUCT CHARACTERISTICS (SmPC)

<table>
<tr><td>1</td><td>Name of the Finished Medicinal Product:</td></tr>
<tr><td>1.1</td><td>Product Name:
Cisatracurium Besylate Injection USP 2 mg/ml (5 ml)</td></tr>
<tr><td>1.2</td><td>Strength : 2 mg/ml</td></tr>
<tr><td>1.3</td><td>Pharmaceutical Form: Injection</td></tr>
<tr><td>2</td><td>Qualitative and Quantitative Compositions:</td></tr>
<tr><td></td><td>Qualitative Declaration:
Active component
INN Name: Cisatracurium Besylate
Quantitative Declaration:
Each ml contains-:
Cisatracurium Besylate USP
Equivalent to Cisatracurium……....2 mg
Water for Injection BP……..q.s

<table>
<tr><th>Sr. No.</th><th>Content Name</th><th>Quality Standard</th><th>Qty per ml</th></tr>
<tr><td>1.</td><td>Cisatracurium Besylate</td><td>USP</td><td>2.68 mg</td></tr>
<tr><td>2.</td><td>Benzene Sulphonic Acid</td><td>IH</td><td># q.s.</td></tr>
<tr><td>3.</td><td>Water For Injection</td><td>BP</td><td>q.s to 1.0 ml</td></tr>
</table>

2.68 mg of Cisatracurium Besylate is equivalent to 2 mg of Cisatracurium
For pH adjustment only.
USP: United States of Pharmacopoeia
IH: In-house Specification
BP: British Pharmacopoeia</td></tr>
<tr><td>3</td><td>Pharmaceutical form: Injection
Description: Clear, colourless liquid.</td></tr>
<tr><td>4</td><td>Clinical Particulars:</td></tr>
<tr><td>4.1</td><td>Therapeutic Indications:
Cisatracurium Besylate Injection 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.</td></tr>
<tr><td>4.2</td><td>Posology and method of administration
Cisatracurium Besylate Injection should only be administered intravenously. The dosage information provided below is intended as a guide only. Doses of Cisatracurium Besylate Injection should be individualized. The use of a peripheral nerve stimulatory will permit the most advantageous use of Cisatracurium Besylate Injection minimize the possibility of over dosage or under dosage, and assist in the evaluation of recovery.</td></tr>
</table>

ADULTS

Initial Doses

One of two intubating doses may be chosen: 0.15 (3 x ED95) and 0.20 (4 x ED95) mg/kg. Doses up to 8 x ED95 Cisatracurium have been safely administered to healthy adult patients and patients with serious cardiovascular disease.

Maintenance Dose

0.03 mg/kg 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 and 50 to 60 minutes following an initial dose of 0.20 mg/kg. The magnitude of these effects may depend on the duration of administration of the volatile agents. The need for maintenance doses should be determined by clinical criteria.

CHILDREN

Initial doses

Children 2 to 12 years of age. Dose is 0.10-0.15 mg/kg administered over 5 to 10 seconds during either halothane or opioid anesthesia. 0.10 mg/kg dose 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). While 0.15 mg/kg dose 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

Infants 1 month to 23 months: Dose is 0.15 mg/kg administered over 5 to 10 seconds.
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

Cisatracurium Besylate Injection can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular block during extended surgical procedures. An initial infusion rate of 3mcg/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.
Reduction of the infusion rate by up to 30% to 40% should be considered when Cisatracurium Besylate is administered during stable Isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen at the 1.25 MAC level). The rate of Infusion of Cisatracurium 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. Base on the structural similarity between Cisatracurium and atracurium, a similar effect on the infusion rate of Cisatracurium may be expected.

INFUSION IN THE INTENSIVE CARE UNIT (ICU)

An infusion rate of approximately 3mcg/kg/min (range: 0.5 to 10.2 mcg/kg/min) should provide adequate neuromuscular block in adult patients in the ICU.

INFUSION RATE TABLES

Tables 1 and 2 provide guidelines for delivery, in ml/hr (equivalent to microdrops/minute 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 for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia for a Concentration of 0.1 mg/mL					
	Drug Delivery Rate (mcg/kg/min)				
	1.0	1.5	2.0	3.0	5.0
Patient Weight (kg)	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 for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia for a Concentration of 0.4 mg/mL					
	Drug Delivery Rate (mcg/kg/min)				
	1.0	1.5	2.0	3.0	5.0
Patient Weight (kg)	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 Contra-indications:

Cisatracurium Besylate Injection is contraindicated in patients known to be hypersensitive to Cisatracurium Besylate, Atracurium or Benzene Sulfonic Acid.

4.4 Special warning and precautions for use:

WARNINGS

Cisatracurium Besylate Injection should be administered in carefully adjusted dosage by or under the supervision of experienced clinicians. The drug should not be administered unless personnel and facilities for resuscitation and life support (tracheal intubation, artificial ventilation, oxygen therapy) and antagonist of Cisatracurium Besylate are immediately available. It is recommended that a peripheral nerve stimulator be used to measure neuromuscular function during the administration. Cisatracurium Besylate Injection has no known effect on consciousness, pain threshold or cerebration. To avoid

	distress to the patient, neuromuscular block should not be induced before unconsciousness. **PRECAUTIONS** Because of its intermediate onset of action, Cisatracurium besylate is not recommended for rapid sequence endotracheal intubation. Recommended doses of Cisatracurium have no clinically significant effects on heart rate; therefore, Cisatracurium 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 myasthenia syndrome). Patients with burns have been shown to develop resistance to nondepolarizing neuromuscular blocking agents, including Atracurium. Patients with hemiparesis or paraparesis also may demonstrate resistance to nondepolarizing muscle relaxants in the affected limbs. Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of 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 0.1mg/kg dose of Cisatracurium Besylate. **Malignant Hyperthermla (MH)** Cisatracurium Besylate has not been studied in MH-susceptible patients **Long-Term use in the Intensive Care Unit (ICU)** Long-term infusion (up to 6 days) of Cisatracurium besylate during mechanical ventilation in the ICU has been safely used in two studies.
4.5	**Interaction with other drugs, other forms of interactions:** Cisatracurium Besylate Injection has been used safely following varying degrees of recovery from succinylcholine-induced neuromuscular block. No drug interactions were observed when vecuronium, pancuronium, or Atracurium were administered following varying degrees of recovery. Isoflurane or enflurane administered with nitrous oxide/oxygen may prolong the clinically effective duration of action of initial and maintenance doses of Cisatracurium Besylate Injection The magnitude of these effects may depend on the duration of administration of the volatile agents. Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Cisatracurium 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.
4.6	**Usage in pregnancy& Lactation** **Pregnancy Category B** There are no adequate and well-controlled studies of Cisatracurium Besylate in pregnant women. Cisatracurium Besylate Injection should be used during pregnancy only if clearly needed. **Labor and Delivery** The use of Cisatracurium Besylate Injection during labor, vaginal delivery, or Cesarean section has not been studied in humans and it is not known whether Cisatracurium administered to the mother has effects on the foetus. **NursingMothers** It is not known whether Cisatracurium Besylate is excreted in human milk. Caution should

	be exercised following administration of Cisatracurium to a nursing woman.
4.7	**Effects on ability to drive and operate machine:** This medicinal product will always be used in combination with a general anaesthetic and therefore the usual precautions relating to performance of tasks following general anaesthesia apply.
4.8	**Undesirable effects:** **Incidence Greater than 1% -** None **Incidence Less than 1%** **Cardiovascular:** bradycardia, hypoension, flushing **Respiratory:** Bronchospasm **Dermatological:** Rash **General:** Histamine release, hypersensitivity reactions including anaphylactic and anaphylactoid responses were severe in rare incidences. There are rare reports of wheezing, laryngospasm, bronchospasm, rash and itching in children. **Musculoskeletal:** Prolonged neuromuscular block, inadequate neuromuscular block, muscle weakness, and myopathy, prolonged recovery.
4.9	**Overdose and special antidotes :** 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 antichlonesterase agent (e.g., neostigmine, edrophonium) in conjuction with an appropriate anticholinergic agent.
5	**Pharmacological Properties:**
5.1	Pharmacodynamic Properties: **Pharmacotherapeutic Group (ATC Code) :** MO3AC11 The neuromuscular blocking activity of Cisatracurium Besylate Injection is due to parent drug. Cisatracurium besylate binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors such as neostigmine.
5.2	**Pharmacokinetic Properties:** Cisatracurium besylate plasma concentration-time data following IV bolus administration are best described by a two-compartment open model. **Distribution** The volume of distribution of Cisatracurium besylate is limited by its large molecular weight and high polarity. The volume of distribution at steady state (Vss) was equal to 145 ml/kg in healthy 19 to 64 year old surgical patients receiving opioid anesthesia. The Vss was 21% larger in similar patients receiving inhalation anesthesia. **Protein Binding** The binding of Cisatracurium besylate to plasma proteins has not been successfully studied due to its rapid degradation at physiologic pH. **Metabolism** The degradation of Cisatracurium besylate is largely independent of liver metabolism. Results from in vitro experiments suggest that Cisatracurium besylate undergoes Hofmann elimination 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 by at a much slower rate than Cisatracurium. Laudanosisne is further metabolized to desmethyl metabolites which are conjugated with glucuronic acid and excreted in the urine. **Elimination** Mean CL values for Cisatracurium besylate 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. In studies of healthy surgical patients, mean $t_{1/2}\beta$ values of Cisatracurium besylate ranged from 22 to 29 minutes and were consistent with the $t_{1/2}\beta$ of Cisatracurium in vitro (29 minutes). The mean ±SD $t_{1/2}\beta$ values of laudanosine were 3.1±0.4 and 3.2 ± 2.1 hours in healthy surgical patients receiving Cisatracurium (n = 10) or Atracurium (n = 10) respectively.
5.3	**Preclinical Safety Data :** **Acute toxicity**: Meaningful acute studies with cisatracurium besylate could not be performed. **Subacute Toxicity**: Studies with repeated administration for three weeks in dogs and monkeys showed no compound specific toxic signs. **Mutagenicity** Cisatracurium besylate was not mutagenic in an in vitro microbial mutagenicity test at concentrations up to 5000 µg/plate. In an in vivo cytogenetic study in rats, no significant chromosomal abnormalities were seen at s.c doses up to 4 mg/kg. Cisatracurium besylate was mutagenic in an in vitro mouse lymphoma cell mutagenicity assay, at concentrations of 40 µg/ml and higher. **Carcinogenicity**: Carcinogenicity studies have not been performed. **Reproductive toxicology**: Reproductive studies in rats have not revealed any adverse effects of cisatracurium besylate on foetal development.
6	**Pharmaceuticals Particulars:**
6.1	**List of Excipients:** Benzene Sulphonic Acid IH Water For Injection BP
6.2	**Incompatibilities:** Y-site Administration 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). Studies have shown that Cisatracurium Injection is compatible with: • 5% Dextrose Injection • 0.9% Sodium Chloride Injection • 5% Dextrose and 0.9% Sodium Chloride Injection • Sufentanil Citrate Injection • Alfentanil Hydrochloride Injection

	• Fentanyl Citrate Injection • Midazolam Hydrochloride Injection • Droperidol Injection Cisatracurium Besylate Injection is not compatible with propofol Injection, ketorolac injection for Y-site administration. Studies of other parental products have not been conducted. **Dilution Stability** Cisatracurium Besylate Injection diluted in 5% Dextrose Injection: 0.9% Sodium Chloride Injection, or 5% Dextrose and 0.9% Sodium chloride Injection, to 0.1 mg/ml may be stored either under refrigeration or at room temperature for 24 hours without significant loss of potency. Diluted Cisatracurium Besylate Injection is chemically and physically stable for at least 12 hours, when stored in either polyvinyl chloride or polypropylene containers, at concentrations between 0.1 and 2.0 mg/ml in the following infusion solutions: • Sodium Chloride (0.9% w/v) Intravenous Infusion • Glucose (5% w/v) Intravenous Infusion • Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion
6.3	**Shelf life:** 18 Months
6.4	**Special precautions for storage:** Store at 2°C to 8°C. Protect from Light. Do not freeze.
6.5	**Nature and contents of container:** Cisatracurium Besylate Injection USP 2 mg/ml is packed in 5 ml USP Type - I amber glass vial with bromo butyl rubber plug and aluminium flip off seal (yellow colour polypropylene disc). 1 such vial packed in a carton along with pack insert.
6.6	**Special precaution for disposal :** Not Applicable
7	**Registrant:** **Marketing Authorization Holder:** **M/s PHILLIPS PHARMACEUTICALS (NIGERIA) LTD.** Address : Afprint Industrial Estate, Plot 122-132, Apapa Oshodi Expressway Lagos Country : Nigeria. Telephone : +234 806761764 Fax : --- E-mail : --- **Manufacturing Site Address:** **M/s THEMIS MEDICARE LIMITED** Sector 6A, Plot No. 16, 17 & 18, IIE, SIDCUL, Haridwar – 249 403, Uttarakhand, INDIA. Telephone: 91-1334-239321/22 Fax: 91-334-239217 E-mail: hwdgmtech@themismedicare.com
8	**Date of Revision of the Text:** Not Applicable

9	**Dosimetry (if applicable):** Not Applicable
10	**Instruction for preparations of Radiopharmaceutical (if applicable):** Not Applicable