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210mm

CISTARIUM®

Solution for Injection/IV

(Cisatracurium Besylate)

For I.V. use only

QUALITATIVE AND QUANTITATIVE COMPOSITION

CISTARIUM® 2mg/ml Solution for Injection/IV (10mg/5ml)
Each ml contains:
Cisatracurium Besylate USP eq. to Cisatracurium.....2mg

PHARMACEUTICAL FORM
Solution for Injection / Infusion.

CLINICAL PARTICULARS
THERAPEUTIC INDICATIONS:
- **CISTARIUM®** is indicated for use during surgical and other procedures in adults and children aged 1 month and over.
- It is also indicated for use in adults requiring intensive care.

Cisatracurium can be used as an adjunct to general anaesthesia, or sedation in the Intensive Care Unit (ICU) to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation.

POSOLOGY AND METHOD OF ADMINISTRATION:
Cisatracurium should only be administered by or under the supervision of anaesthetists or other clinicians who are familiar with the use and action of neuromuscular blocking agents. Facilities for tracheal intubation, and maintenance of pulmonary ventilation and adequate arterial oxygenation have to be available. Please note that cisatracurium should not be mixed in the same syringe or administered simultaneously through the same needle as propofol injectable emulsion or with alkaline solutions such as sodium thiopentone. Cisatracurium contains no antimicrobial preservative and is intended for single patient use. **Monitoring advice:** As with other neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of cisatracurium in order to individualize dosage requirements.
Posology: Use by intravenous bolus injection:
Dosage in Adults: ***Tracheal intubation:*** 0.15mg/kg (body weight). This dose produced good to excellent conditions for tracheal intubation 120 seconds after administration of cisatracurium, following induction of anaesthesia with propofol; higher doses will shorten the time to onset of neuromuscular block. ***Maintenance:*** Neuromuscular block can be extended with maintenance doses of cisatracurium. A dose of 0.03mg/kg (body weight) provides approximately 20 minutes of additional clinically effective neuromuscular block during opioid or propofol anaesthesia; consecutive maintenance doses do not result in progressive prolongation of effect. ***Spontaneous recovery:*** Once spontaneous recovery from neuromuscular block is underway, the rate is independent of the cisatracurium dose administered. During opioid or propofol anaesthesia, the median times from 25 to 75% and from 5 to 95% recovery are approximately 13 and 30 minutes, respectively. ***Reversal:*** Neuromuscular block following cisatracurium administration is readily reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T_4:T_1 ratio ≥0.7) are approximately 4 and 9 minutes respectively, following administration of the reversal agent at an average of 10% T_1 recovery.
Dosage in Paediatrics: ***Tracheal intubation (paediatric patients aged 1 month to 12 years):*** As in adults, the recommended intubation dose of cisatracurium is 0.15mg/kg (body weight) administered rapidly over 5 to 10 seconds; this dose produces good to excellent conditions for tracheal intubation 120 seconds following injection of cisatracurium. There are limited known data on the use of cisatracurium in paediatric patients under 2 years of age undergoing prolonged or major surgery. In paediatric patients aged 1 month to 12 years, cisatracurium has a shorter clinically effective duration and a faster spontaneous recovery profile than those observed in adults under similar anaesthetic conditions. ***When cisatracurium is not required for intubation:*** A dose of less than 0.15mg/kg can be used; administration of cisatracurium following suxamethonium is not known to be studied in paediatric patients. Halothane may be expected to extend the clinically effective duration of a dose of cisatracurium by up to 20%. No information is available on the use of cisatracurium in children during anaesthesia with other halogenated fluorocarbon anaesthetic agents, but these agents may also be expected to extend the clinically effective duration of a dose of cisatracurium. ***Maintenance (paediatric patients aged 2 to 12 years):*** Neuromuscular block can be extended with maintenance doses of cisatracurium. In paediatric patients aged 2 to 12 years, a dose of 0.02mg/kg (body weight) provides approximately 9 minutes of additional clinically effective neuromuscular block during halothane anaesthesia. Consecutive maintenance doses do not result in progressive prolongation of effect; there are insufficient data to make a specific recommendation for maintenance dosing in paediatric patients under 2 years of age. However, very limited data from clinical studies in paediatric patients under 2 years of age suggest that a maintenance dose of 0.03mg/kg may extend clinically effective neuromuscular block for a period of up to 25 minutes during opioid anaesthesia. ***Spontaneous recovery:*** Once recovery from neuromuscular block is underway, the rate is independent of the cisatracurium dose administered. During opioid or halothane anaesthesia, the median times from 25 to 75% and from 5 to 95% recovery are approximately 11 and 28 minutes, respectively. ***Reversal:*** Neuromuscular block following cisatracurium administration is readily reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T_4:T_1 ratio ≥0.7) are approximately 2 and 5 minutes respectively, following administration of the reversal agent at an average of 13% T_1 recovery.
Use by intravenous infusion: ***Dosage in adults and children aged 2 to 12 years:*** ● Maintenance of neuromuscular block may be achieved by infusion of cisatracurium. ● An initial infusion rate of 3mcg/kg (body weight)/min (0.18mg/kg/h) is recommended to restore 89 to 99% T_1 suppression following evidence of spontaneous recovery. After an initial period of stabilization of neuromuscular block, a rate of 1 to 2mcg/kg (body weight)/min (0.06 to 0.12mg/kg/h) should be adequate to maintain block in this range in most patients. ● Reduction of the infusion rate by up to 40% may be required when cisatracurium is administered during isoflurane or enflurane anaesthesia. ● The infusion rate will depend upon the concentration of cisatracurium in the infusion solution, the desired degree of neuromuscular block, and the patient's weight.
Cisatracurium 2mg/ml infusion rate:

Patient body weight (kg)	Dose (mcg/kg/min)				Infusion rate
	1.0	1.5	2.0	3.0	
20	0.6	0.9	1.2	1.8	mL/h
70	2.1	3.2	4.2	6.3	
100	3.0	4.5	6.0	90	

● Steady rate continuous infusion is not associated with a progressive increase or decrease in neuromuscular blocking effect.
● Following discontinuation of infusion, spontaneous recovery from neuromuscular block proceeds at a rate comparable to that following administration of a single bolus.
Dosage in Intensive Care Unit (ICU) patients: ● Cisatracurium may be administered by bolus dose and/or infusion to adult patients in the ICU. ● An initial infusion rate of cisatracurium of 3mcg/kg (body weight)/min (0.18mg/kg/h) is recommended for adult ICU patients. There may be wide interpatient variation in dosage requirements and these may increase or decrease with time. In clinical studies, the average infusion rate was 3mcg/kg/min [range 0.5 to 10.2mcg/kg (body weight)/min (0.03 to 0.6mg/kg/h)]. ● The median time to full spontaneous recovery following long-term (up to 6 days) infusion of cisatracurium in ICU patients was approximately 50 minutes. ● The recovery profile after infusions of cisatracurium to ICU patients is independent of duration of infusion.
Special Patient Groups: ***Dosage in elderly patients:*** No dosing alterations are required in elderly patients. ***Dosage in patients with renal impairment:*** No dosing alterations are required in patients with renal failure. In these patients cisatracurium has a similar pharmacodynamic profile to that observed in patients with normal renal function but it may have a slightly slower onset. ***Dosage in patients with hepatic impairment:*** No dosing alterations are required in patients with end-stage liver disease. In these patients cisatracurium has a similar pharmacodynamic profile to that observed in patients with normal hepatic function but it may have a slightly faster onset. ***Dosage in patients with cardiovascular disease:*** When administered by rapid bolus injection (over 5 to 10 seconds) to adult patients with serious cardiovascular disease (New York Heart Association Class I-III) undergoing coronary artery bypass graft (CABG) surgery, cisatracurium has not been associated with clinically significant cardiovascular effects at any dose studied (up to and including 0.4mg/kg (8 x ED_{95}s). However, there are limited data for doses above 0.3mg/kg in this patient population). Cisatracurium has not been studied in children undergoing cardiac surgery. ***Dosage in neonates (aged less than 1 month):*** The use of cisatracurium in neonates is not recommended as it has not been studied in this patient population.

CONTRAINDICATIONS:
Hypersensitivity to cisatracurium, atracurium or benzene sulfonic acid.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Product specific topics: ● Cisatracurium paralyses the respiratory muscles as well as other skeletal muscles but has no known effect on consciousness or pain threshold. ● Cisatracurium should be only administered by or under the supervision of anaesthetists or other clinicians who are familiar with the use and action of neuromuscular blocking agents. Facilities for tracheal intubation, and maintenance of pulmonary ventilation and adequate arterial oxygenation have to be available. ● Caution should be exercised when administering cisatracurium to patients who have shown hypersensitivity to other neuromuscular blocking agents. ● Cisatracurium does not have significant vagolytic or ganglion-blocking properties. Consequently, cisatracurium will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery. ● Patients with myasthenia gravis and other forms of neuromuscular disease have shown greatly increased sensitivity to non-depolarizing blocking agents. An initial dose of not more than 0.02mg/kg is recommended in these patients. ● Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking agents. ● Cisatracurium in neonates aged less than one month has not been studied in this population. ● Cisatracurium has not known to be studied in patients with a history of malignant hyperthermia. ● There have been no studies known of cisatracurium in patients undergoing surgery with induced hypothermia (25 to 28°C). ● Cisatracurium has not known to be studied in patients with burns; however, as with other non-depolarizing neuromuscular blocking agents, the possibility of increased dosing requirements and shortened duration of action must be considered if cisatracurium injection is administered to these patients. ● Cisatracurium is hypotonic solution and must not be applied into the infusion line of a blood transfusion.
Intensive Care Unit (ICU) patients: ● Laudanosine, a metabolite of cisatracurium and atracurium, has been associated with transient hypotension and in some species, cerebral excitatory effects. There have been rare reports of seizures in ICU patients who have received atracurium and other agents. These patients usually had one or more medical conditions predisposing to seizures (e.g., cranial trauma, hypoxic encephalopathy, cerebral oedema, viral encephalitis, uremia). A causal relationship to laudanosine has not been established.

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INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Many drugs have been shown to influence the magnitude and/or duration of action of non-depolarizing neuromuscular blocking agents, including the following:
Increased effect: ● Anaesthetic agents such as enflurane, isoflurane, halothane and ketamine; ● Non-depolarizing neuromuscular blocking agents; ● Antibiotics (including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin); ● Antiarrhythmic drugs (including propranolol, calcium channel blockers, lidocaine, procainamide and quinidine); ● Diuretics, (including furosemide and possibly thiazides, mannitol and acetazolamide); ● Magnesium and lithium salts; ● Ganglion blocking drugs (trimetaphan, hexamethonium).
Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; such drugs include various antibiotics, beta blockers (propranolol, oxprenolol), antiarrhythmic drugs (procainamide, quinidine), antirheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium. **Decreased effect:** ● A decreased effect is seen after prior chronic administration of phenytoin or carbamazepine. ● Treatment with anticholinesterases, commonly used in the treatment of Alzheimer's disease (e.g., donepezil), may shorten the duration and diminish the magnitude of neuromuscular blockade with cisatracurium.
No effect: Prior administration of suxamethonium has no effect on the duration of neuromuscular block following bolus doses of cisatracurium or on infusion rate requirements.

FERTILITY, PREGNANCY AND LACTATION:
Fertility: Fertility studies have not been performed. **Pregnancy:** There are no adequate data from the use of cisatracurium in pregnant women. The potential risk for humans is unknown. Cisatracurium should not be used during pregnancy. **Breast-feeding:** It is not known whether cisatracurium or its metabolites are excreted in human milk. As a precaution breast-feeding should be discontinued during treatment for at least five elimination half-lives of cisatracurium, i.e., for about 3 hours after the last dose or the end of infusion of cisatracurium.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
This precaution is not relevant to the use of cisatracurium.

UNDESIRABLE EFFECTS:
Common: Bradycardia, hypotension. **Uncommon:** Cutaneous flushing, bronchospasm, rash. **Very rare:** Anaphylactic reaction, anaphylactic shock; Anaphylactic reactions of varying degrees of severity are known to be observed after the administration of neuromuscular blocking agents, including anaphylactic shock. Very rarely, severe anaphylactic reactions have been reported in patients receiving cisatracurium in conjunction with one or more anaesthetic agents, myopathy, muscle weakness; There have been some reports of muscle weakness and/or myopathy following prolonged use of muscle relaxants in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids. These events have been reported infrequently in association with cisatracurium and a causal relationship has not been established.

OVERDOSE:
Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage with cisatracurium. It is essential to maintain pulmonary ventilation and arterial oxygenation until adequate spontaneous respiration returns. Full sedation will be required since consciousness is not impaired by cisatracurium. Recovery may be accelerated by the administration of anticholinesterase agents once evidence of spontaneous recovery is present.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Muscle relaxants, peripherally acting agents, other quaternary ammonium compounds. **ATC code:** M03AC11.
Cisatracurium is an intermediate-duration, non-depolarizing benzylisoquinolinium skeletal muscle relaxant.
Mechanism of action: Cisatracurium binds to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a competitive block of neuromuscular transmission. This action is readily reversed by anticholinesterase agents such as neostigmine or edrophonium. The ED_{95} (dose required to produce 95% depression of the twitch response of the adductor pollicis muscle to stimulation of the ulnar nerve) of cisatracurium is estimated to be 0.05mg/kg bodyweight during opioid anaesthesia (thiopentone/fentanyl/midazolam). The ED_{95} of cisatracurium in children during halothane anaesthesia is 0.04mg/kg.

PHARMACOKINETIC PROPERTIES:
Biotransformation: Cisatracurium undergoes degradation in the body at physiological pH and temperature by Hofmann elimination (a chemical process) to form laudanosine and the monoquaternary acrylate metabolite. **Elimination:** Elimination of cisatracurium is largely organ independent but the liver and kidneys are primary pathways for the clearance of its metabolites. These metabolites do not possess neuromuscular blocking activity. **Pharmacokinetics in adult patients:** Non-compartmental pharmacokinetics of cisatracurium are independent of dose in the range studied (0.1 to 0.2mg/kg, i.e., 2 to 4 x ED_{95}). Population pharmacokinetic modelling confirms and extends these findings up to 0.4mg/kg (8 x ED_{95}). Pharmacokinetic parameters after doses of 0.1 and 0.2mg/kg cisatracurium administered to healthy adult surgical patients are summarized in the table below:

Parameter	Range of mean values
Clearance	4.7 to 5.7mL/min/kg
Volume of distribution at steady state	121 to 161mL/kg
Elimination half-life	22 to 29min

Pharmacokinetics in elderly patients: No clinically important differences in the pharmacokinetics of cisatracurium in elderly and young adult patients. The recovery profile is also unchanged. **Pharmacokinetics in patients with renal/hepatic impairment:** No clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage renal failure or end-stage liver disease and in healthy adult patients. Their recovery profiles are also unchanged. **Pharmacokinetics during infusions:** The pharmacokinetics of cisatracurium after infusions of cisatracurium are similar to those after single bolus injection. The recovery profile after infusion of cisatracurium is independent of duration of infusion and is similar to that after single bolus injection. **Pharmacokinetics in Intensive Care Unit (ICU) patients:** The pharmacokinetics of cisatracurium in ICU patients receiving prolonged infusions are known to be similar to those in healthy surgical adults receiving infusions or single bolus injections. The recovery profile after infusions of cisatracurium in ICU patients is independent of duration of infusion. Concentrations of metabolites are higher in ICU patients with abnormal renal and/or hepatic function. These metabolites do not contribute to neuromuscular block.

PHARMACEUTICAL PARTICULARS

INCOMPATIBILITIES: Degradation of cisatracurium besylate has been demonstrated to occur more rapidly in lactated Ringer's Injection and 5% Dextrose and lactated Ringer's Injection than in the infusion fluids mentioned below. Therefore, it is recommended that lactated Ringer's Injection and 5% Dextrose and lactated Ringer's Injection are not used as the diluent in preparing solutions of Cisatracurium for infusion. Since cisatracurium is stable only in acidic solutions it should not be mixed in the same syringe or administered simultaneously through the same needle with alkaline solutions (e.g., sodium thiopentone). It is not compatible with ketorolac trometamol or propofol injectable emulsion.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:
For single use only. The medicinal product should be used immediately after opening the ampoule. The medicinal product should be visually inspected prior to use. This medicine should not be used if there are any visible signs of deterioration (e.g., particles). Diluted cisatracurium solution is physically and chemically stable for at least 24 hours at 5°C and 25°C at concentrations between 0.1mg/ml and 1.5mg/ml in the following infusion fluids when in contact with polypropylene or polycarbonate syringes, polyethylene or PVC tubing, and polypropylene or PVC infusion bags:
○ Sodium chloride 0.9% solution; ○ Glucose 5% solution; ○ Sodium chloride 0.18% and glucose 4% solution; ○ Sodium chloride 0.45% and glucose 2.5% solution.
Cisatracurium has been shown to be compatible with the following commonly used perioperative drugs, when mixed in conditions simulating administration into a running intravenous infusion via a Y-site injection port: alfentanil hydrochloride, droperidol, fentanyl citrate, midazolam hydrochloride and sufentanil citrate.
Where other drugs are administered through the same needle or cannula as cisatracurium, it is recommended that each drug be flushed through with an adequate volume of a suitable intravenous fluid, e.g., sodium chloride 0.9% solution. As with other drugs administered intravenously, when a small vein is selected as the injection site, cisatracurium should be flushed through the vein with a suitable intravenous fluid, e.g., sodium chloride 0.9% solution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
CISTARIUM® 2mg/ml Solution for Injection/IV (10mg/5ml) in a pack of 5's

INSTRUCTIONS
Dosage: As directed by the physician.
To be sold on the prescription of a physician only. Keep out of reach of children.
Store at 2 to 8°C, and protect from heat, light and freezing.
Once removed from the refrigerator to room temperature (25°C), use within 21 days even if re-refrigerated. Improper storage may deteriorate the medicine.
Injection should not be used if container is leaking, solution is cloudy or it contains undissolved particle(s).

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

سسٹیریم® سلوشن برائے انجکشن/ آئی وی
(سساٹراکیوریم)
بینزیلیٹ

ہدایات: خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف ڈاکٹر کے نسخے کے مطابق فروخت کریں۔ بچوں کی پہنچ سے دور رکھیں۔
دوا کو ۲ سے ۸ ڈگری سینٹی گریڈ پر رکھیں اور گرمی، روشنی اور منجمد ہونے سے محفوظ رکھیں۔
ریفریجریٹر سے نکالنے کے بعد کمرے کے درجہ حرارت (۲۵ ڈگری سینٹی گریڈ)
پر لانے اور دوبارہ ریفریجریٹر میں رکھنے کی صورت میں ۲۱ دن کے اندر استعمال کر لیں
ورنہ دوا خراب ہو جائیگی۔

انجکشن کے لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل
پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔

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