Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cisatracurium 2 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 2 mg of cisatracurium (as cisatracurium besilate).
Each 2.5 ml ampoule contains 5 mg of cisatracurium.
Each 5 ml ampoule contains 10 mg of cisatracurium.
Each 10 ml ampoule contains 20 mg of cisatracurium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion

Clear, colourless or yellowish solution, free from visible particles.
pH of solution 3.0-3.8

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cisatracurium 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.

4.2 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. (see section 6.2).

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 individualise dosage requirements.

Posology

1.Use by intravenous bolus injection

Dosage in adults

Tracheal intubation
The recommended intubation dose of cisatracurium for adults is 0.15 mg/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.

The following table summarises mean pharmacodynamic data when cisatracurium was administered at doses of 0.1 to 0.4 mg/kg (body weight) to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

Table 1 Mean pharmacodynamic data following a range of cisatracurium doses

Initial dose mg/kg (body weight)	Anaesthetic background	Time to 90% T1* suppression (minutes)	Time to maximum T1* suppression (minutes)	Time to 25% spontaneous T1*recovery (minutes)
0.1	Opioid	3.4	4.8	45
0.15	Propofol	2.6	3.5	55
0.2	Opioid	2.4	2.9	65
0.4	Opioid	1.5	1.9	91

* T1 Single twitch response as well as the first component of the train-of-four response of the adductor pollicis muscle following supramaximal electrical stimulation of the ulnar nerve.

Enflurane or isoflurane anaesthesia may extend the clinically effective duration of an initial dose of cisatracurium by as much as 15%.

Maintenance
Neuromuscular block can be extended with maintenance doses of cisatracurium. A dose of 0.03 mg/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 (T4:T1 ratio ≥0.7) are approximately 4 and 9 minutes respectively, following administration of the
reversal agent at an average of 10% T1 recovery.

Dosage in paediatric patients

Tracheal intubation (paediatric patients aged 1 month to 12 years)
As in adults, the recommended intubation dose of cisatracurium is 0.15 mg/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. Pharmacodynamic data for this dose are presented in the tables below (Table 2, Table 3 and Table 4).

Cisatracurium has not been studied for intubation in ASA Class III-IV paediatric patients. There are limited 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. Small differences in the pharmacodynamic profile were observed between the age ranges 1 to 11 months and 1 to 12 years which are summarised in the Table 2 and Table 3.

Table 2 Paediatric patients aged 1 to 11 months

Cisatracurium dose mg/kg (body weight)	Anaesthetic background	Time to 90% suppression (minutes)	Time to maximum suppression (minutes)	Time to 25% spontaneous T1 recovery (minutes)
0.15	Halothane	1.4	2.0	52

0.15	Opioid	1.4	1.9	47

Table 3 Paediatric patients aged 1 to 12 years

Cisatracurium dose mg/kg (body weight)	Anaesthetic background	Time to 90% suppression (minutes)	Time to maximum suppression (minutes)	Time to 25% spontaneous T1 recovery (minutes)
0.15	Halothane	2.3	3.0	43
0.15	Opioid	2.6	3.6	38

When cisatracurium is not required for intubation: a dose of less than 0.15 mg/kg can be used. Pharmacodynamic data for doses of 0.08 and 0.1 mg/kg for paediatric patients aged 2 to 12 years are presented in the Table 4.

Table 4 Paediatric patients aged 2 to 12 years

Cisatracurium dose mg/kg (body weight)	Anaesthetic background	Time to 90% suppression (minutes)	Time to maximum suppression (minutes)	Time to 25% spontaneous T1 recovery (minutes)
0.08	Halothane	1.7	2.5	31
0.1	Opioid	1.7	2.8	28

Administration of cisatracurium following suxamethonium has not been studied in paediatric patients (see section 4.5).

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 0.02 mg/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 0.03 mg/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 (T4:T1 ratio ≥0.7) are approximately 2 and 5 minutes respectively, following administration of the reversal agent at an average of 13% T1 recovery.

1.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 3 micrograms/kg (body weight)/min (0.18 mg/kg/h) is recommended to restore 89 to 99% T1 suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 to 2 micrograms/kg (body weight)/min (0.06 to 0.12 mg/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 (see section 4.5).

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. Table below provides guidelines for delivery of undiluted Cisatracurium 2 mg/ml solution for injection/infusion.

Table 5 Cisatracurium 2 mg/ml infusion rate

Patient body weight (kg)	Dose (microgram/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	ml/h
100	3.0	4.5	6.0	9.0	ml/h

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 3 micrograms/kg (body weight)/min (0.18 mg/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 3 micrograms/kg/min [range 0.5 to 10.2 micrograms/kg (body weight)/min (0.03 to 0.6 mg/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. In these patients cisatracurium has a similar pharmacodynamic profile to that observed in young adult patients but, as with other neuromuscular blocking agents, it may have a slightly slower onset.

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 0.4 mg/kg (8 x ED_{95})). However, there are limited data for doses above 0.3 mg/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.

Method of administration

For intravenous use.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to cisatracurium, atracurium or benzenesulfonic acid or to any of the excipients listed in section 6.1.

4.4 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 since a high rate of cross-sensitivity (greater than 50%) between neuromuscular blocking agents has been reported (see section 4.3).

Cisatracurium does not have significant vagolytic or ganglion-blocking properties. Consequently, cisatracurium has no clinically significant effect on heart rate and 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-depolarising blocking agents. An initial dose of not more than 0.02 mg/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.

There is no information on the use of cisatracurium in neonates aged less than one month since it has not been studied in this patient population.

Cisatracurium has not been studied in patients with a history of malignant hyperthermia. Studies in malignant hyperthermia-susceptible pigs indicated that cisatracurium does not trigger this syndrome.

There have been no studies of cisatracurium in patients undergoing surgery with induced hypothermia (25 to 28°C). As with other neuromuscular blocking agents the rate of infusion required to maintain adequate surgical relaxation under these conditions may be expected to be significantly reduced.

Cisatracurium has not been studied in patients with burns; however, as with other non-depolarising 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
When administered to laboratory animals in high doses, laudanosine, a metabolite of cisatracurium and atracurium, has been associated with transient hypotension and in some species, cerebral excitatory effects. In the most sensitive animal species, these effects occurred at laudanosine plasma concentrations similar to those that have been observed in some ICU patients following prolonged infusion of atracurium.

Consistent with the decreased infusion rate requirements of cisatracurium, plasma laudanosine concentrations are approximately one third those following atracurium infusion.

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, uraemia). A causal
relationship to laudanosine has not been established.

4.5 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-depolarising neuromuscular blocking agents, including the following:

Increased effect:
-by anaesthetic agents such as enflurane, isoflurane, halothane (see section 4.2) and ketamine;
-by other non-depolarising neuromuscular blocking agents;
-by other drugs such as 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; increased sensitivity to non-depolarising neuromuscular blocking agents might result. Such drugs include various antibiotics, beta blockers (propranolol, oxprenolol), antiarrhythmic drugs (procainamide, quinidine), antirheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

Administration of suxamethonium to prolong the effects of non-depolarising neuromuscular blocking agents may result in a prolonged and complex block which can be difficult to reverse with anticholinesterases.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of cisatracurium in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (see section 5.3). 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. A risk to the breastfed infant cannot be excluded. However, due to the short half-life, an influence on the breastfed infant is not to be expected if the mother restarts breast-feeding after the effects of the substance have worn off. As a precaution breast-feeding should be discontinued during treatment and it is recommended to abstain from next breastfeeding for five elimination half- lives of cisatracurium, i.e. for about 3 hours after the last dose or the end of infusion of cisatracurium.

Fertility
Fertility studies have not been performed.

4.7 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.

4.8 Undesirable effects

The following convention has been used for the classification of frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Immune system disorders
Very rare: Anaphylactic reaction, anaphylactic shock

Anaphylactic reactions of varying degrees of severity have been 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.

Cardiac disorders
Common: Bradycardia

Vascular disorders
Common: Hypotension
Uncommon: Cutaneous flushing

Respiratory, thoracic and mediastinal disorders
Uncommon: Bronchospasm

Skin and subcutaneous tissue disorders
Uncommon: Rash

Musculoskeletal and connective tissue disorders
Very rare: 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms and signs
Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage with cisatracurium.

Management
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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: muscle relaxants, peripherally acting agents, other quaternary ammonium compounds, ATC code: M03AC11

Cisatracurium is an intermediate-duration, non-depolarising benzylisoquinolinium skeletal muscle relaxant for intravenous administration.

Mechanism of action
Clinical studies in man indicated that cisatracurium is not associated with dose dependent histamine release even at doses up to and including 8 x ED_{95}.
Cisatracurium binds to cholinergic receptors on the motor end-plate to antagonise 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 0.05 mg/kg bodyweight during opioid anaesthesia (thiopentone/fentanyl/midazolam).

The ED_{95} of cisatracurium in children during halothane anaesthesia is 0.04 mg/kg.

5.2 Pharmacokinetic properties

Biotransformation/elimination
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. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite. 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 0.2 mg/kg, i.e. 2 to 4 x ED_{95}).
Population pharmacokinetic modelling confirms and extends these findings up to 0.4 mg/kg (8 x ED_{95}). Pharmacokinetic parameters after doses of 0.1 and 0.2 mg/kg cisatracurium administered to healthy adult surgical patients are summarised in the table below:

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

Pharmacokinetics in elderly patients
There are 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
There are 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 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 (see section 4.4). These metabolites do not contribute to neuromuscular block.

5.3 Preclinical safety data

Acute toxicity
For symptoms of toxicity see section 4.9.

Subacute toxicity
Studies with repeated administration for three weeks in dogs and monkeys showed no compound specific toxic signs.

Mutagenicity
Cisatracurium was not mutagenic in an *in vitro* microbial mutagenicity test at concentrations up to 5000 micrograms/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 was mutagenic in an *in vitro* mouse lymphoma cell mutagenicity assay, at concentrations of 40 micrograms/ml and higher. A single positive mutagenic response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Carcinogenicity
Carcinogenicity studies have not been performed.

Reproductive toxicology
Fertility studies have not been performed. Reproductive studies in rats have not revealed any adverse effects of cisatracurium on foetal development.

Local tolerance
The result of an intra-arterial study in rabbits showed that cisatracurium injection is well tolerated and no drug related changes were seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzenesulfonic acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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.

6.3 Shelf life

Unopened ampoule: 18 months

Shelf life after dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and 25°C (see section 6.6).
From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Store and transport refrigerated (2°C - 8°C). Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2.5 ml, 5 ml or 10 ml of solution filled in type I colourless glass ampoules with one point cut.
Ampoules are marked with a specific colour ring code for each volume.
Five ampoules are placed into a PVC liner. Liner is placed into a carton.

Not all pack sizes may be marketed.

6.6 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 is physically and chemically stable for at least 24 hours at 2-8°C and 25°C at concentration 0.1 mg/ml in the following infusion fluids when in contact with polypropylene or polycarbonate syringes, polyethylene or PVC tubing, and polypropylene or PVC infusion bags:

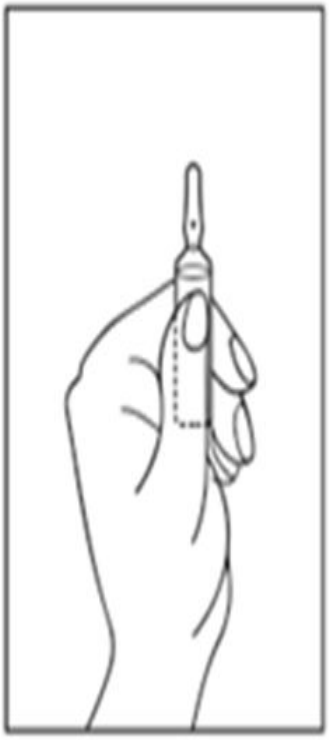
-sodium chloride 9 mg/ml (0.9%) solution for injection;
-glucose 50 mg/ml (5%) solution for injection;
-sodium chloride 1.8 mg/ml (0.18%) and glucose 40 mg/ml (4%) solution for injection;
-sodium chloride 4.5 mg/ml (0.45%) and glucose 25 mg/ml (2.5%) solution for injection.

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 9 mg/ml (0.9%) solution for injection.

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 9 mg/ml (0.9%) solution for injection.

<u>Instruction of ampoule opening:</u>

1. Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2. Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AS Kalceks
Krustpils Iela 71e
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

PA2165/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th September 2019

10 DATE OF REVISION OF THE TEXT

March 2022