Cisatracurium-hameln 2 mg/ml solution for injection/infusion

1. NAME OF THE MEDICINAL PRODUCT

Cisatracurium-hameln 2 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection/infusion contains 2.677 mg cisatracurium besilate equivalent to 2 mg cisatracurium.

1 ampoule of 2.5 ml solution for injection/infusion contains 6.7 mg cisatracurium besilate equivalent to 5 mg cisatracurium.

1 ampoule of 5 ml solution for injection/infusion contains 13.4 mg cisatracurium besilate equivalent to 10 mg cisatracurium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion

Clear, colourless to pale yellow or greenish yellow solution with a pH of 3.0-3.8.

After dilution: Clear, colourless to pale yellow or greenish yellow solution, free of visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Cisatracurium-hameln is an intermediate-duration, non-depolarising neuromuscular blocking agent for intravenous (i.v.) administration.

Cisatracurium-hameln is indicated for use during surgical and other procedures and in intensive care. It is 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.

Cisatracurium-hameln contains no antimicrobial preservative and is intended for single patient use.

4.2. Posology and method of administration

Parenteral preparation for intravenous administration.

As with other neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of cisatracurium-hameln in order to individualise dosage requirements.

Use by I.V. bolus injection in adults

Tracheal Intubation

The recommended intubation dose of cisatracurium for adults 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.

Higher doses will shorten the time to onset of neuromuscular block.

Table 1 summarises mean pharmacodynamic data when cisatracurium was administered at doses of 0.1 to 0.4 mg/kg to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

Table 1: Mean Pharmacodynamic Data Following a Range of Cisatracurium Doses

Initial cisatracurium dose (mg/kg)	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

* 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 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 more than or equal to 0.7) are approximately 2 and 5 minutes, respectively, following administration of the reversal agent at an average of 13% T1 recovery.

Use by I.V. bolus injection in children (aged 2 to 12 years of age)

Tracheal Intubation

The recommended initial intubation dose of cisatracurium in children aged 2 to 12 years is 0.1 mg/kg administered over 5 to 10 seconds. The following table summarises mean pharmacodynamic data obtained during opioid anaesthesia. A dose of 0.1 mg/kg has a faster onset time, a shorter clinical effective duration and a faster spontaneous recovery profile than those observed in adults under similar anaesthesia conditions.

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

Halothane may be expected to extend the clinically effective duration of cisatracurium by up to 20%.

No information is available on the use of cisatracurium in children during isoflurane or enflurane anaesthesia but these agents may also be expected to extend the clinically effective duration of a dose of cisatracurium by up to 20%.

Although tracheal intubation has not been specifically studied in this age group, onset is faster than in adults and therefore intubation should also be possible within two minutes of administration.

Maintenance

Neuromuscular block can be extended with maintenance doses of cisatracurium. A dose of 0.02 mg/kg provides approximately 9 minutes of additional clinically effective neuromuscular block during halothane anaesthesia.

Consecutive maintenance doses do not result in progressive prolongation of effect.

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 more than or equal to 0.7) are approximately 2 and 5 minutes respectively, following administration of the reversal agent at an average 13% T1 recovery.

Use by I.V. infusion 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/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/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 Interactions).

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 2 provides guidelines for delivery of undiluted cisatracurium.

Table 2: Infusion Delivery Rate of cisatracurium 2 mg/mL:

Patient weight (kg)	Dose (micrograms/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.

Neonates aged less than 2 years

No dosage recommendation for paediatric patients under 2 years of age can be made until further information becomes available.

Elderly

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.

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.

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.

Patients with cardiovascular disease

Cisatracurium has been used effectively to provide neuromuscular block in patients undergoing cardiac surgery. When administered by rapid bolus injection (over 5 to 10 seconds) to patients with serious cardiovascular disease cisatracurium has not been associated with clinically significant cardiovascular effects at any dose studied (up to and including 0.4 mg/kg ($8xED_{95}$)).

ICU patients

Cisatracurium may be administered by bolus dose and/or infusion to adult patients in the ICU.

An initial infusion rate of 3 micrograms/kg/min (0.18 mg/kg/h) is recommended for adult ICU patients. There may be wide inter-patient variation in dosage requirements and these may increase or decrease with time.

The median time to full spontaneous recovery following long-term (up to 6 days) infusion in ICU patients is approximately 50 minutes.

The recovery profile after infusions to ICU patients is independent of duration of infusion.

Patients undergoing hypothermic cardiac surgery

There have been no studies of cisatracurium in patients undergoing surgery with induced hypothermia (25°C 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.

4.3. Contraindications

Hypersensitivity to cisatracurium, atracurium or benzenesulfonic acid.

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.

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 newborn infants 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, but there are no indications that cisatracurium does 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 require-

ments and shortened duration of action must be considered if cisatracurium is administered to these patients.

Cisatracurium-hameln is hypotonic and must not be applied into the infusion line of a blood transfusion.

Intensive Care Unit (ICU) Patients

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, a metabolite of cisatracurium and atracurium, has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Many medicinal products 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 medicinal products such as antibiotics (including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin),
- by antiarrhythmics (including propranolol, calcium channel blockers, lidocaine, procainamide and quinidine),
- by diuretics, (including furosemide and possibly thiazides, mannitol and acetazolamide),
- by magnesium and lithium salts and
- by ganglion blocking agents (trimetaphan, hexamethonium).

A decreased effect is seen after preceding chronic administration of phenytoin or carbamazepine.

Preceding administration of suxamethonium has no effect on the duration of neuromuscular block following bolus doses of cisatracurium or on infusion rate requirements.

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.

Rarely, certain medicinal products may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to non-depolarising neuromuscular blocking agents might result. Such agents include various antibiotics, betablockers (propranolol, oxprenolol), antiarrhythmics (procainamide, quinidine), antirheumatics (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of cisatracurium in pregnant women.

Cisatracurium-hameln should not be used during pregnancy.

Breastfeeding

It is not known whether cisatracurium or its metabolites are excreted in human milk.

A risk to the breastfed infant cannot be excluded. 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 breastfeeding 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.

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

Immune system disorders:

Very rare: Anaphylactic reactions, anaphylactic shock

Anaphylactic reactions of varying degrees of severity have been observed after the administration of muscle relaxants, 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.

4.9 Overdose

Symptoms and signs

Prolonged muscle paralysis and its consequences are expected to be the main signs of overdose 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 anti-cholinesterase agents once evidence of spontaneous recovery is present.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Muscle relaxants, peripherally acting agents; other quaternary ammonium compound

ATC code: M03AC11

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

Cisatracurium is not associated with dose dependent histamine release even at doses up to and including $8xED_{95}$

Mechanism of action

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 anti-cholinesterase 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.

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.

Pharmacokinetic 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 $4xED_{95}$).

Population pharmacokinetic modelling confirms and extends these findings up to 0.4 mg/kg ($8xED_{95}$). 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 are similar to those after single bolus injection. The recovery profile after infusion 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzenesulfonic acid 1% (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: 2 years

Shelf life after first opening:

The product should be used immediately after opening the ampoule.

Prepared infusion solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

6.4 Special precautions for storage

Store in a refrigerator (2-8°C).

Do not freeze.

Keep ampoules in the outer carton in order to protect from light.

Keep out of reach of children.
Jauhi daripada kanak-kanak.

6.5 Nature and contents of container

3 ml and 5 ml colourless, type I glass ampoules

Pack sizes:

10 Ampoules x 2.5 ml

10 Ampoules x 5 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Diluted to a concentration of 0.1 mg cisatracurium/ml, Cisatracurium-hameln is physically and chemically stable for 24 hours at 25°C in sodium chloride 9 mg/ml (0.9%) solution; in sodium chloride 9 mg/ml (0.9%) and glucose 50 mg/ml (5%) solution; and in glucose 50 mg/ml (5%) solution.

Cisatracurium has been shown to be compatible with the following commonly used peri-operative medicinal products, 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 agents are administered through the same indwelling needle or cannula as Cisatracurium-hameln, it is recommended that each medicinal product be flushed through with an adequate volume of a suitable intravenous fluid, e.g., sodium chloride 9 mg/ml (0.9%) solution.

7. MANUFACTURED BY:

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