Package leaflet: Information for the user

Cisatracurium 2 mg/ml solution for injection/infusion

Cisatracurium

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cisatracurium is and what it is used for

Cisatracurium 2 mg/ml solution for injection/infusion contains a medicine called cisatracurium.This belongs to a group of medicines called muscle relaxants.

Cisatracurium is used:

- to relax muscles during operations on adults and children over 1 month of age, including heart surgery
- to help insert a tube into the windpipe (tracheal intubation), if a person needs help to breathe
- to relax the muscles of adults in intensive care.

Ask your doctor if you would like more explanation about this medicine.

2. What you need to know before you are given Cisatracurium

Do not use cisatracurium

- if you are allergic to cisatracurium, any other muscle relaxant or any of the other ingredients in Cisatracurium 2 mg/ml solution for injection/infusion (listed in section 6)
- you have reacted badly to an anaesthetic before.

Do not have Cisatracurium if any of the above apply to you. If you are not sure, talk to your doctor, nurse or pharmacist before you have Cisatracurium.

Take special care with Cisatracurium
Talk to your doctor, nurse or pharmacist before having this medcine:
- if you have muscle weakness, tiredness or difficulty in co-ordinating your movements (myasthenia gravis)
- you have a neuromuscular disease, such as a muscle wasting disease, paralysis, motor neurone disease or cerebral palsy
- if you have a burn which requires medical treatment

- you have ever had an allergic reaction to any muscle relaxant which was given as part of an operation.

If you are not sure if any of the above apply to you, talk to your doctor, nurse or pharmacist before you are given Cisatracurium.

Other medicines and Cisatracurium
Tell your doctor if you are taking or have recently taken any other medicines. This includes any herbal products or medicines bought without a prescription.
In particular tell your doctor if you are taking any of the following:
- anaesthetics (used to reduce sensation and pain during surgical procedures)
- antibiotics (used to treat infections)
- medicines for uneven heart beats (anti-arrhythmics)
- medicines for high blood pressure
- water tablets (diuretics), such as furosemide
- medicines for inflammation of the joints, such as chloroquine or d-penicillamine
- steroids
- medicines for fits (epilepsy), such as phenytoin or carbamazepine
- medicines for mental illness, such as lithium or chlorpromazine (which can also be used for sickness)
- medicines containing magnesium
- drugs for Alzheimer's disease (anticholinesterases e.g. donepezil).

Pregnancy and breast-feeding
Do not breast feed for at least 3 hours after your last dose when the effects of cisatracurium have worn off.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
If you are only staying in hospital for the day, your doctor will tell you how long to wait before leaving the hospital or driving a car. It can be dangerous to drive too soon after having an operation.

3. How Cisatracurium is given

How your injection is given
You will never be expected to give yourself this medicine. It will always be given to you by a person who is qualified to do so.

Cisatracurium can be given:
- as a single injection into your vein (intravenous bolus injection)
- as a continuous infusion into your vein. This is where the drug is slowly given to you over a long period of time.

Your doctor will decide the way you are given the drug and the dose you will receive. It will depend on:
- your body weight
- the amount and duration of muscle relaxation required
- your expected response to the medicine.

Children less than 1 month old should not have this medicine.

If you receive more Cisatracurium than you should

Cisatracurium will always be given under carefully controlled conditions. However, if you think that you have been given more than you should tell your doctor or nurse immediately.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, Cisatracurium can cause side effects, although not everybody gets them.
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

Allergic reactions (affects less than 1 in 10,000 people)
If you have an allergic reaction, tell your doctor or nurse straight away. The signs may include:

- sudden wheeziness, chest pain or chest tightness
- swelling of your eyelids, face, lips, mouth or tongue
- a lumpy skin rash or 'hives' anywhere on your body
- a collapse and shock.

Talk to your doctor, nurse or pharmacist if you notice any of the following:

Common (affects less than 1 in 10 people)
- decrease in heart rate
- decrease in blood pressure.

Uncommon (affects less than 1 in 100 people)
- a rash or redness of your skin
- wheezing or coughing.

Very rare (affects less than 1 in 10,000 people)
- weak or aching muscles.

Reporting of side effects

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cisatracurium

- Keep Cisatracurium out of the sight and reach of children.
- Do not use Cisatracurium after the expiry date shown on the pack after 'Exp'.
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- Store in the original package in order to protect from light.
- If diluted, store the infusion solution between 2°C and 8°C and use within 24 hours. Any unused infusion solution should be discarded 24 hours after it was prepared.
- Do not throw away any medicines via wastewater or household waste. Your doctor or nurse will throw away any medicine that is no longer required. This will help protect the environment.

6. Contents of the pack and other information

What Cisatracurium contains

• The active substance is 2 mg/ml cisatracurium (as besilate).

• The other ingredients are benzene sulfonic acid and Water for Injections.

What Cisatracurium looks like and contents of the pack

Cisatracurium 2 mg/ml solution for injection/infusion is a colourless or light yellow or yellow-green clear solution. Each glass vial is packed in individual carton.
2.5 ml of the solution contains 5 mg of Cisatracurium.
5 ml of the solution contains 10 mg of Cisatracurium.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
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Information for the Physician:

Please refer to the Summary of Product Characteristics (SPC) for further details on this product.

Name of the medicinal product

Cisatracurium 2 mg/ml solution for injection/infusion

Qualitative and quantitative composition

Cisatracurium 2 mg/ml solution for injection/infusion contains:
Cisatracurium 2 mg as cisatracurium besilate 2.68 mg per 1 ml
One vial of 2.5 ml contains 5 mg of cisatracurium
One vial of 5 ml contains 10 mg of cisatracurium

Pharmaceutical form

Solution for injection/infusion

Colourless or light yellow or yellow-green clear solution. Practically free from visible particulate matter.

Therapeutic indications

Cisatracurium is indicated for use during surgical and other procedures in adults and children aged 1 month and over. Cisatracurium 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 individualise dosage requirements.

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.

Table 1 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 Cisatracurium 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 2, 3 and 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 tables 2 and 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 below:

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.

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 2-12 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 anti-cholinesterase 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.

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 µg/kg (body weight)/min (0.18 mg/kg/hr) 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 µg/kg (body weight)/min (0.06 to 0.12 mg/kg/hr) 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. Table 5 provides guidelines for delivery of undiluted Cisatracurium.

Table 5: Infusion Delivery Rate of Cisatracurium injection 2 mg/ml

Patient (body weight) (kg)	Dose (µg/kg/min)				Infusion Rate
	1.0	1.5	2.0	3.0	
20	0.6	0.9	1.2	1.8	ml/hr
70	2.1	3.2	4.2	6.3	ml/hr
100	3.0	4.5	6.0	9.0	ml/hr

Steady rate continuous infusion of Cisatracurium is not associated with a progressive increase or decrease in neuromuscular blocking effect.

Following discontinuation of infusion of Cisatracurium, spontaneous recovery from neuromuscular block proceeds at a rate comparable to that following administration of a single bolus.

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.

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 (8x ED95)). 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 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 µg/kg (body weight)/min (0.18 mg/kg/hr) 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 µg/kg/min [range 0.5 to 10.2 µg/kg (body weight)/min (0.03 to 0.6mg/kg/hr)].
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.

Contraindications

Cisatracurium is contra-indicated in patients known to be hypersensitive to cisatracurium, atracurium, or benzene sulfonic acid.

Special warnings and precautions for use

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.

Great 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 Cisatracurium 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 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 (eg. cranial trauma, hypoxic encephalopathy, cerebral oedema, viral encephalitis, uraemia). A causal relationship to laudanosine has not been established.

Pharmaceutical particulars

Benzene sulfonic acid
Water for injections

Shelf life

Shelf life before dilution: 18 months.

Chemical and physical in-use stability has been demonstrated for 30 hours at 5°C and 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 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Store in a refrigerator (2°C- to 8°C). Do not freeze.
Store in the original package in order to protect from light.
For storage conditions of the diluted medicinal product see section 5 of the Package Leaflet.

Instructions for use/handling

This product is for single use only. Use only colourless or light yellow or yellow-green clear solutions. The product should be visually inspected before use, and if the visual appearance has changed or if the container is damaged, the product must be discarded.

Diluted Cisatracurium is physically and chemically stable for 30 hours at 5°C and 25°C at concentrations between 0.1 and 2 mg/ml in the following infusion fluids.

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.
Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion.

However, since the product contains no antimicrobial preservative, dilution should be carried out immediately prior to use, or failing this be stored as directed under section 5 of the Package Leaflet.

Cisatracurium has been shown to be compatible with the following commonly used peri-operative 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 indwelling 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 Intravenous Infusion (0.9% w/v).

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 intravenous infusion (0.9% w/v).

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