## APPROVED PROFESSIONAL INFORMATION

## SCHEDULING STATUS: S4

## 1. NAME OF THE MEDICINE

**CISATRACURIUM 5 mg/2,5 ml FRESENIUS**

**CISATRACURIUM 10 mg/5 ml FRESENIUS**

**CISATRACURIUM 20 mg/10 ml FRESENIUS**

Solution for injection or infusion (2 mg/ml)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 2 mg cisatracurium (as the besilate).

**Cisatracurium 5 mg/2,5 ml Fresenius**: Each 2,5 ml ampoule contains 5 mg cisatracurium.

**Cisatracurium 10 mg/5 ml Fresenius:** Each 5 ml ampoule contains 10 mg cisatracurium.

**Cisatracurium 20 mg/10 ml Fresenius:** Each 10 ml ampoule contains 20 mg cisatracurium.

Sugar free.

For the full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear, pale yellow or greenish yellow solution, practically free from visible particles. 3

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

CISATRACURIUM FRESENIUS 2 mg/ml is used during surgical procedures to relax skeletal muscles and to facilitate controlled ventilation.

CISATRACURIUM FRESENIUS 2 mg/ml is suitable for endotracheal intubation especially where subsequent muscle relaxation is required.

## 4.2 Posology and method of administration

Use by intravenous bolus injection:

**Dosage in adults:**

***Tracheal intubation***: The recommended intubation dose of CISATRACURIUM FRESENIUS 2 mg/ml Injection for adults is 0,15 mg/kg. 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. The following table summarises mean pharmacodynamic data when cisatracurium besilate injection was administered at doses of 0,1 to 0,4 mg/kg to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

| **Initial cisatracurium besilate dose (mg/kg)** | **Anaesthetic background** | **Time to 90 % $T_1$[a] suppression (min)** | **Time to maximum $T_1$[a] suppression (min)** | **Time to 25 % Spontaneous $T_1$[a] recovery (min)** |
|---|---|---|---|---|
| 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 |

[a] 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.

***Maintenance***:

Neuromuscular block can be extended with maintenance doses of CISATRACURIUM FRESENIUS 2 mg/ml injection. 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 FRESENIUS 2 mg/ml dose. 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 FRESENIUS 2 mg/ml administration is reversible with standard doses of anticholinesterase medicines. The mean times from 25 to 75 % recovery and to full clinical recovery ($T_4$:$T_1$ ratio $\geq$ 0,7) are approximately 4 and 9 minutes respectively, following administration of the reversal medicine at an average of 10 % $T_1$ recovery.

**Dosage in paediatric patients aged 1 month to 12 years:**

***Tracheal intubation*:**

As in adults, the recommended intubation dose of CISATRACURIUM FRESENIUS 2 mg/ml injection is 0,15 mg/kg administered rapidly over 5 to 10 seconds. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection of CISATRACURIUM FRESENIUS 2 mg/ml. Pharmacodynamic data for this dose are presented in the tables below. If a shorter clinical duration is required, pharmacodynamic data suggest that a dose of 0,1 mg/kg may produce similar intubation conditions at 120 to 150 seconds.

In paediatric patients aged 1 month to 12 years, CISATRACURIUM FRESENIUS 2 mg/ml 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 below.

**Paediatric patients aged 1 to 11 months**

| Initial cisatracurium besilate dose (mg/kg) | Anaesthetic background | Time to 90 % suppression (min) | Time to maximum suppression | Time to 25 % spontaneous T1 recovery (min) |
|---|---|---|---|---|
| 0,15 | Halothane | 1,4 | 2,0 | 52 |
| 0,15 | Opioid | 1,4 | 2,0 | 47 |

**Paediatric patients aged 1 to 12 years**

| Initial cisatracurium besilate dose (mg/kg) | Anaesthetic background | Time to 90 % suppression (min) | Time to maximum suppression (min) | Time to 25 % spontaneous $T_1$ recovery (min) |
|---|---|---|---|---|
| 0,08 | Halothane | 1,7 | 2,5 | 31 |
| 0,1 | Opioid | 1,7 | 2,8 | 28 |
| 0,15 | Halothane | 2,3 | 3,0 | 43 |
| 0,15 | Opioid | 2,6 | 3,6 | 38 |

Halothane may be expected to extend the clinically effective duration of a dose of CISATRACURIUM FRESENIUS 2 mg/ml by up to 20 %. No information is available on the use of CISATRACURIUM FRESENIUS 2 mg/ml in children during isoflurane anaesthesia but these medicines may also be expected to extend the clinically effective duration of a dose of CISATRACURIUM FRESENIUS 2 mg/ml by up to 20 %.

***Maintenance***:

Neuromuscular block can be extended with maintenance doses of CISATRACURIUM FRESENIUS 2 mg/ml injection. 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 ¡s independent of the CISATRACURIUM FRESENIUS 2 mg/ml 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 FRESENIUS 2 mg/ml administration is reversible with standard doses of anticholinesterase medicines. The mean times from 25 to 75 % recovery and to full clinical recovery ($T_4$:$T_1$ ratio $\geq$ 0,7) are approximately 2 and 5 minutes respectively, following administration of the reversal medicine 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 FRESENIUS 2 mg/ml injection. An initial infusion rate of 3 µg/kg/min (0,18 mg/kg/hr) is recommended to restore 89 to 99% $T_1$ suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 to 2 µg/kg/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 FRESENIUS 2 mg/ml injection 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. The following table provides guidelines for delivery of undiluted CISATRACURIUM FRESENIUS 2 mg/ml injection.

**Infusion delivery rate of CISATRACURIUM FRESENIUS 2 mg/ml injection 2 mg/ml**

| Patient 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 FRESENIUS 2 mg/ml injection is not associated with a progressive increase or decrease in neuromuscular blocking effect.

Following discontinuation of infusion of CISATRACURIUM FRESENIUS 2 mg/ml injection, spontaneous recovery from neuromuscular block proceeds at a rate comparable to that following administration of a single bolus.

## Special populations:

**Dosage in neonates aged less than 1 month:**

No dosage recommendation for neonates can be made until further information becomes available.

**Dosage in elderly patients:**

No dosing alterations are required in elderly patients. In these patients CISATRACURIUM FRESENIUS 2 mg/ml injection has a similar pharmacodynamic profile to that observed in young adult patients, but as with other neuromuscular blocking medicines, 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 FRESENIUS 2 mg/ml injection 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 FRESENIUS 2 mg/ml injection has a similar pharmacodynamic profile to that observed ¡n patients with normal hepatic function but it may have a slightly faster onset.

**Dosage in patients with cardiovascular disease:**

CISATRACURIUM FRESENIUS 2 mg/ml has been used 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 FRESENIUS 2 mg/ml has not been associated with clinically significant cardiovascular effects in any dose studied (up to and including 0,4 mg/kg (8 x $ED_{95}$)).

**Dosage in Intensive Care Unit (ICU) patients**:

CISATRACURIUM FRESENIUS 2 mg/ml may be administered by bolus dose and/or infusion to adult patients in the ICU. An initial infusion rate of CISATRACURIUM FRESENIUS 2 mg/ml of 3 µg/kg/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/mm (range 0,5 to 10,2 µg/kg/min (0,03 to 0,6 mg/kg/hr). The median time to full spontaneous recovery following long-term (up to 6 days) infusion of cisatracurium besilate in ICU patients was approximately 50 minutes.

**Infusion delivery rate of CISATRACURIUM FRESENIUS 2 mg/ml injection 5 mg/ml**

| Patient Weight (kg) | Dose (µg/kg/mm) | | | | Infusion Rate |
|---|---|---|---|---|---|
| | 1,0 | 1,5 | 2,0 | 3,0 | |
| 70 | 0,8 | 1,2 | 1,7 | 2,5 | ml/hr |
| 100 | 1,2 | 1,8 | 2,4 | 3,6 | ml/hr |

The recovery profile after infusions of CISATRACURIUM FRESENIUS 2 mg/ml to ICU patients is independent of duration of infusion.

**Dosage in patients undergoing hypothermic cardiac surgery:**

There have been no studies of CISATRACURIUM FRESENIUS 2 mg/ml injection in patients undergoing surgery with induced hypothermia (25 to 28°C). The rate of infusion required to maintain adequate surgical relaxation under these conditions may be expected to be significantly reduced.

**Dilution**:

See section 6.6.

## 4.3 Contraindications

- Patients known to be hypersensitive to cisatracurium, atracurium, or benzenesulphonic acid, or any of the ingredients in CISATRACURIUM FRESENIUS 2 mg/ml (see section 6.1).
- Neonates, as CISATRACURIUM FRESENIUS 2 mg/ml injection has not been studied in this patient population.
- Use and safety in pregnancy and lactation have not been established.

## 4.4 Special warnings and precautions for use

**CISATRACURIUM PARALYSES THE RESPIRATORY MUSCLES AS WELL AS OTHER SKELETAL MUSCLES BUT HAS NO EFFECT ON CONSCIOUSNESS OR PAIN THRESHOLD. CISATRACURIUM FRESENIUS 2 mg/ml INJECTION SHOULD ONLY BE ADMINISTERED BY OR UNDER THE SUPERVISION OF AN ANAESTHETIST.**

**FACILITIES FOR TRACHEAL INTUBATION, AND MAINTENANCE OF PULMONARY VENTILATION AND ADEQUATE ARTERIAL OXYGENATION HAVE TO BE AVAILABLE.**

**MONITORING OF NEUROMUSCULAR FUNCTION IS RECOMMENDED DURING THE USE OF CISATRACURIUM FRESENIUS 2 mg/ml INJECTION IN ORDER TO INDIVIDUALISE DOSAGE REQUIREMENTS.**

CISATRACURIUM FRESENIUS 2 mg/ml is hypotonic and must not be administered into the infusion line of a blood transfusion.

Great caution should be exercised when administering CISATRACURIUM FRESENIUS 2 mg/ml to patients who have shown hypersensitivity to other neuromuscular blocking substances, since a high rate of cross-sensitivity between neuromuscular blocking substances has been reported (see section 4.3).

Cisatracurium does not have significant vagolytic or ganglion- blocking properties. Consequently, CISATRACURIUM FRESENIUS 2 mg/ml has no clinically significant effect on heart rate and will not counteract the bradycardia produced by many anaesthetic medicines 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 medicines. An initial dose of not more than 0,02 mg/kg CISATRACURIUM FRESENIUS 2 mg/ml is recommended in these patients.

Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking substances.

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

Cisatracurium has not been studied in patients with burns; however, as with other non-depolarising neuromuscular blocking substances, the possibility of increased dosing requirements and shortened duration of action must be considered if CISATRACURIUM FRESENIUS 2 mg/ml is administered to these patients.

There is no information on the use of CISATRACURIUM FRESENIUS 2 mg/ml in neonates aged less than one month since it has not been studied in this patient population.

ICU patients:

As per reported studies, when laudanosine, a metabolite of cisatracurium, was administered to experimental animals, high concentrations were associated with hypotension and, in some species, cerebral excitation.

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

There have been reports of seizures in ICU patients who have received atracurium and other medicines. 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 medicines and other forms of interaction

Many medicines have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking medicines, including the following:-

Increased effect:

By anaesthetic medicines such as enflurane, isoflurane, halothane (see section 4.2) and ketamine, by other non- depolarising neuromuscular blocking medicines or by other medicines such as antibiotics (including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin), antidysrhythmic medicines (including propranolol, calcium channel blockers, lidocaine, procainamide and quinidine), diuretics, (including furosemide and possibly thiazides, mannitol and acetazolamide), magnesium and lithium salts and ganglion blocking medicines (trimetaphan, hexamethonium).

**C**ertain medicines may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to non-depolarising neuromuscular blocking medicines might result. Such medicines include various antibiotics, beta-blockers (propranolol, oxprenolol), antidysrhythmic medicines (procainamide, quinidine), anti-rheumatic medicines (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

Administration of suxamethonium to prolong the effects of non- depolarising neuromuscular blocking medicines 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 FRESENIUS 2 mg/ml or on infusion rate requirements.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Use and safety in pregnancy has not been established (see section 4.3).

CISATRACURIUM FRESENIUS 2 mg/ml should therefore not be used during pregnancy.

Breastfeeding

Use and safety in lactation has not been established (see section 4.3). CISATRACURIUM FRESENIUS 2 mg/ml should therefore not be used during breastfeeding.

Fertility

Fertility studies have not been performed.

## 4.7 Effects on ability to drive and use machines

CISATRACURIUM FRESENIUS 2 mg/ml will always be used in combination with a general anaesthetic and can therefore have a major influence on the ability to drive and use machines. The patient must not drive or operate machines following anaesthesia with CISATRACURIUM FRESENIUS 2 mg/ml.

## 4.8 Undesirable effects

Tabulated list of adverse reactions

| | |
|---|---|
| **Immune system disorders** | |
| Frequency unknown | Anaphylactic reaction |
| **Cardiac disorders** | |
| Frequent | Bradycardia |

| | |
|---|---|
| **Vascular disorders** | |
| Frequent | Hypotension |
| Less frequent | Cutaneous flushing |
| **Musculoskeletal and connective tissue disorders** | |
| Frequency unknown | Myopathy, muscle weakness |
| **Respiratory, thoracic and mediastinal disorders** | |
| Less frequent | Bronchospasm |
| **Skin and subcutaneous tissue disorders** | |
| Less frequent | Rash |

## Description of selected adverse reactions

Anaphylactic reactions of varying degrees of severity have been observed after the administration of neuromuscular blocking medicines. Severe anaphylactic reactions have been reported in patients receiving CISATRACURIUM FRESENIUS 2 mg/ml in conjunction with one or more anaesthetic substances.

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 FRESENIUS 2 mg/ml and a causal relationship has not been established.

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug

Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

## 4.9 Overdose

Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage with CISATRACURIUM FRESENIUS 2 mg/ml.

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 FRESENIUS 2 mg/ml. Recovery may be accelerated by the administration of anticholinesterase medicines once evidence of spontaneous recovery is present.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Category A, Class 17.1 - Peripherally-acting muscle relaxants

### Mechanism of action

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

### Pharmacodynamic effects

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 medicines such as neostigmine or edrophonium.

## 5.2 Pharmacokinetic properties

### Biotransformation

Cisatracurium undergoes degradation in the body at physiological pH and temperature by Hofmann elimination to form laudanosine and the monoquaternary acrylate rnetabolite. The

monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite.

These metabolites do not possess neuromuscular blocking activity.

## Elimination

Elimination of cisatracurium is largely organ independent but the liver and kidneys are primary pathways for the clearance of its metabolites.

## Pharmacokinetics in adult patients

The $ED_{95}$ (dose required to produce 95% depression of the twitch response of the adductor pollicise 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 ED95 of cisatracurium besilate in children during halothane anaesthesia is 0,04mg/kg. 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 $ED_{95}$).

**Pharmacokinetic parameters after doses of 0,1 and 0,2 mg/kg CISATRACURIUM FRESENIUS 2 mg/ml injection administered to healthy adult surgical patients are summarised in the table below**:

| **Parameter** | **Range of mean values** |
|---|---|
| Clearance | 47 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.

Pharmacokinetics in patients with renal impairment:

There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage renal failure and in healthy adult patients. The recovery profile of cisatracurium is unchanged in the presence of renal failure.

Pharmacokinetics in patients with hepatic impairment:

There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage liver disease and in healthy adult patients. The recovery profile was unchanged.

Pharmacokinetics during infusions:

The pharmacokinetics of cisatracurium after infusions of CISATRACURIUM FRESENIUS 2 mg/ml injection are similar to those after single bolus injection. The recovery profile after infusion of CISATRACURIUM FRESENIUS 2 mg/ml injection is independent of duration of infusion and ¡s similar to that after single bolus injections.

Pharmacokinetics in 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 FRESENIUS 2 mg/ml in ICU patients is independent of duration of infusion. When laudanosine was administered to experimental animals, high concentrations were associated with hypotension and, in some species, cerebral excitation.

However, there is no evidence that laudanosine has caused such effects in man even after prolonged infusions of cisatracurium to ICU patients with impaired renal and/or hepatic function.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Benzenesulphonic acid 1 % m/m (pH adjustment) and water for injection (solvent).

## 6.2 Incompatibilities

CISATRACURIUM FRESENIUS 2 mg/ml is not chemically stable when diluted with Lactated Ringer's injection.

Since CISATRACURIUM FRESENIUS 2 mg/ml 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

This product is marketed as a single dose ampoule and any unused portion of the solution must be discarded.

**Diluted solution**:

Chemical and physical in-use stability has been demonstrated for at least 24 hours at 5 °C (± 3 °C) and 25 °C (see section 6.6).

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.

## 6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C). Do not freeze. Store in the original package to protect from light. The ampoule must not be removed from the outer carton until such time as it is required for administration.

For storage conditions of the diluted product, see section 6.3.

## 6.5 Nature and contents of container

CISATRACURIUM FRESENIUS 2 mg/ml solution for injection/infusion

Type 1, clear, colourless glass ampoules:

5 mg in 3 ml: 1, 5, 10 or 50 3 ml-ampoules.

10 mg in 5 ml: 1, 5, 10 or 50 in 5 ml-ampoules.

20 mg in 10 ml: 1, 5, 10 or 50 in 10 ml-ampoules.

The ampoules are packaged in a cardboard box with an instruction leaflet.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

CISATRACURIUM FRESENIUS 2 mg/ml is for single use only.

Use only clear and almost colourless up to slightly yellow/greenish yellow coloured 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 FRESENIUS 2 mg/ml is physically and chemically stable for at least 12 hours at 5 °C and 25 °C, at concentrations between 0,1 and 2,0 mg/ml in the following infusion fluids, in either polyvinyl chloride (PVC) or polypropylene containers:

Sodium chloride (0,9 % m/v) intravenous infusion, glucose (5 % m/v) intravenous infusion, sodium chloride (0,18 % m/v) and glucose (4 % m/v) intravenous infusion, sodium chloride (0,45 % m/v) and glucose (2,5 % m/v) intravenous infusion. However, since the product contains no antimicrobial preservative dilution should be carried out immediately prior to use, administration should commence as soon as possible, thereafter and any remaining solution should be discarded.

CISATRACURIUM FRESENIUS 2 mg/ml has been shown to be compatible with the following commonly used peri-operative medicines, 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 medicines are administered through the same indwelling needle or cannula as CISATRACURIUM FRESENIUS 2 mg/ml, it is recommended that each medicine be flushed through with an adequate volume of a suitable intravenous fluid, e.g., sodium chloride intravenous infusion 0,9 % (m/v).

When a small vein is selected as the injection site, CISATRACURIUM FRESENIUS 2 mg/ml should be flushed through the vein with a suitable intravenous fluid, e.g., sodium chloride intravenous infusion (0,9 % m/v).

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7, Midrand

1685

South Africa

## 8. REGISTRATION NUMBERS

Cisatracurium 5 mg/2,5 ml Fresenius: 47/17.1/0292

Cisatracurium 10 mg/5 ml Fresenius: 47/17.1/0293

Cisatracurium 20 mg/10 ml Fresenius: 47/17.1/0294

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 29 June 2021

## 10. DATE OF REVISION OF THE TEXT