NAME OF THE DRUG
Cisatracurium-AFT contains Cisatracurium besylate

The chemical name of cisatracurium besylate is 
(1R,1′R,2R,2′R,)-2,2′-(3,11-dioxo-4,10-dioxatridecamethylene) bis (1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisooquinolinium) dibenzenesulfonate. The molecular formula of cisatracurium besylate is \( \text{C}_{65}\text{H}_{82}\text{N}_{2}\text{O}_{18}\text{S}_{2} \) and it has a molecular weight of 1243.5. The structural formula is given below:

![Structural formula of Cisatracurium besylate](image)

CAS Number: 96946-42-8

DESCRIPTION
Cisatracurium besylate is a white to yellowish powder.

Cisatracurium-AFT is supplied in two strengths, either 2 mg or 5 mg (as the besylate salt) of cisatracurium besylate per mL. Cisatracurium-AFT also contains Water for Injections and benzenesulfonic acid. Cisatracurium-AFT does not contain any antimicrobial preservative and is intended for single patient use on one occasion only. Discard any residue.

PHARMACOLOGY

Pharmacodynamics
Cisatracurium besylate, a stereoisomer of atracurium, is an intermediate duration, non-depolarising benzylisoquinolinium skeletal muscle relaxant. Cisatracurium besylate 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.
The ED\textsubscript{95} (dose required to produce 95% depression of the twitch response of the adductor pollicis muscle to stimulation of the ulnar nerve) of cisatracurium besylate is estimated to be 0.05 mg/kg bodyweight during opioid anaesthesia (thiopentone, fentanyl, midazolam). The recommended intubation dose for cisatracurium in adults is 3 x ED\textsubscript{95}, which has a longer clinically effective duration than the recommended intubation dose of atracurium (2 x ED\textsubscript{95}) (see DOSAGE AND ADMINISTRATION).

The ED\textsubscript{95} of cisatracurium besylate in children during halothane anaesthesia is 0.04 mg/kg bodyweight.

Cisatracurium besylate undergoes degradation in the body at physiological pH and temperature by Hofmann elimination 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 besylate 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 besylate are independent of dose in the range studied (0.1 to 0.2 mg/kg bodyweight; i.e., 2 to 4 x ED\textsubscript{95}). Population pharmacokinetic modelling confirms and extends these findings up to 0.4 mg/kg bodyweight (8 x ED\textsubscript{95}). Pharmacokinetic parameters after doses of 0.1 and 0.2 mg/kg bodyweight cisatracurium Injection administered to healthy adult surgical patients are summarised below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range of mean values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>4.7 to 5.7 mL/min/kg</td>
</tr>
<tr>
<td>Volume of distribution at steady state</td>
<td>121 to 161 mL/kg</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>22 to 29 min</td>
</tr>
</tbody>
</table>

**Pharmacokinetics during infusions**

The pharmacokinetics of cisatracurium besylate following infusion of Cisatracurium-AFT is similar to those following a single bolus injection. Pharmacokinetics were studied in healthy adult surgical patients who received an initial 0.1 mg/kg bolus dose of cisatracurium injection followed by a maintenance infusion of cisatracurium to maintain 89 to 99% T\textsubscript{1} suppression. Mean clearance of cisatracurium besylate was 6.9 mL/kg/min and the elimination half-life was 28 minutes. During infusion of cisatracurium besylate peak plasma concentrations of laudanosine and the monoquaternary alcohol metabolites are approximately 6% and 11% of the parent compound, respectively.

The recovery profile after infusion of cisatracurium is independent of the duration of infusion and is similar to that after single bolus injection.

**Pharmacokinetics in Intensive Care Unit (ICU) patients**

The pharmacokinetics of cisatracurium besylate in ICU patients receiving prolonged infusion is similar to those in healthy surgical adults receiving infusion or single bolus injection. Mean clearance of cisatracurium besylate was 7.5 mL/kg/min and the elimination half-life was 27 minutes. 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 functions (see PRECAUTIONS). These metabolites do not contribute to neuromuscular block.

**Pharmacokinetics in elderly patients**

There are no clinically important differences in the pharmacokinetics of cisatracurium besylate in elderly patients. In a comparative study plasma clearance was unaffected by age. Minor differences in volume of distribution (+17%) and half-life (+4 min) did not affect the recovery profile.

**Pharmacokinetics in paediatric patients**

No full study has been performed to assess the pharmacokinetics of cisatracurium in paediatric patients.

The population pharmacokinetics/pharmacodynamics of cisatracurium was described in 20 healthy paediatric patients during halothane anaesthesia, using the same model developed for healthy adult patients. The clearance was higher in healthy paediatric patients (5.89 mL/min/kg) than in healthy adult patients (4.57 mL/min/kg) during opioid anaesthesia. The rate of equilibration between plasma concentrations and neuromuscular block, as indicated by $k_{es}$, was faster in healthy paediatric patients receiving halothane anaesthesia (0.1330 minutes$^{-1}$) than in healthy adult patients receiving opioid anaesthesia (0.0575 minutes$^{-1}$). The EC$_{50}$ in healthy paediatric patients (125 ng/mL) was similar to the value in healthy adult patients (141 ng/mL) during opioid anaesthesia. The minor differences in the pharmacokinetic/ pharmacodynamic parameters of cisatracurium were associated with a faster time to onset and a shorter duration of cisatracurium-induced neuromuscular block in paediatric patients.

**Pharmacokinetics in patients with renal impairment**

There are no clinically important differences in the pharmacokinetics of cisatracurium besylate in patients with end-stage renal failure. In a comparative study there were no statistically significant or clinically important differences in pharmacokinetic parameters of cisatracurium besylate. The recovery profile of cisatracurium besylate 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 besylate in patients with end-stage liver disease. In a comparative study of patients undergoing liver transplantation and healthy adults there were small differences in volume of distribution (+21%) and clearance (+16%). There were no differences in the elimination half-life of cisatracurium besylate. The recovery profile was unchanged.

**CLINICAL TRIALS**

The cisatracurium clinical development programme was constructed to provide for systematic collection of efficacy and safety data and to ensure exposure to therapeutically relevant doses of cisatracurium in various populations of patients undergoing a diversity of surgical procedures during opioid, propofol or inhalation anaesthesia as well as ICU patients who require neuromuscular blocking agents to facilitate mechanical ventilation. The result was 23 clinical trials conducted in 1295 surgical and ICU patients administered cisatracurium and 255 patients administered control neuromuscular blocking agents (atracurium or vecuronium). A total of 20 of these
studies contributed efficacy data and included 1206 patients administered cisatracurium. All studies contributed safety data.

The major populations of patients were classified by the American Society of Anesthesiologists (ASA) Classification or New York Heart Association (NYHA) Classification as:

- Healthy (ASA Class 1 or 2) young adult (aged 18-50 years), elderly adult (aged 65-89) and paediatric patients (aged 1 month-12 years).
- Seriously ill (ASA Class 3 or 4) elderly patients or patients with end-stage renal or hepatic disease.
- Seriously ill (NYHA Class I to IV) adult patients with serious cardiovascular disease scheduled for Coronary Artery Bypass Graft (CABG) surgery.
- Critically ill adult ICU patients requiring neuromuscular blocking agents to facilitate mechanical ventilation.

The studies included 660 healthy adult patients, 236 paediatric patients (aged 2-12 years), 110 paediatric patients (aged 1-23 months), 15 patients with end-stage liver disease (ESLD), 17 patients with end-stage renal failure (ESRF), 182 patients with serious cardiovascular disease (undergoing coronary artery bypass graft surgery) and 68 critically ill patients in the ICU. Forty-eight elderly patients (≥ 65 years) were specifically studied in two studies. Overall, 172 (13%) of the patients administered cisatracurium were ≥ 65 years.

The most common types of surgical procedures were urological (28% of cisatracurium patients) and CABG (14% of cisatracurium patients). Other types of procedures included general surgery (11%), gynaecological (7%), neurosurgical (5%), orthopaedic (8%), oral (3%), plastic (2%), ear, nose and throat (3%) and vascular (1%). ICU patients accounted for 5% of patients administered cisatracurium. There were no obstetric studies.

The clinical development programme acquired substantive data in regard to efficacy and safety of large bolus doses of cisatracurium. The mean clinically effective dose of cisatracurium (ED₉₅) estimated from two dose-response studies of adult patients receiving opioid anaesthesia was 0.05 mg/kg. Of the 1295 patients to whom cisatracurium was administered in clinical trials, 102 (8%) received initial bolus doses < ED₉₅, 649 (50%) received initial bolus doses in the ED₉₅ to 2 x ED₉₅ range, and 515 (40%) received initial doses that exceeded 2 x ED₉₅. ICU patients had neuromuscular block initiated with an infusion and/or bolus dose.

Following the initial dose of cisatracurium, many patients received one or more additional bolus doses, continuous intravenous (iv) infusion, or both to maintain an adequate level of neuromuscular block. The use of cisatracurium by continuous infusion during surgical procedures requiring extended neuromuscular block was investigated in healthy (ASA Class 1 or 2) adult patients in 7 studies. The majority of patients received cisatracurium by infusion during opioid anaesthesia, the duration of infusion ranging from 11-261 minutes. Maintenance dose data for cisatracurium were captured in 6 studies, a total of 154 adult surgical patients being administered 1-21 maintenance doses of 0.03 mg/kg.

The adequacy of intubation conditions following cisatracurium was assessed in 5 studies in a total of 480 patients (aged 1 month to 87 years) administered cisatracurium.
INDICATIONS
Cisatracurium-AFT is indicated for use during surgical and other procedures and in intensive care to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation. It is used as an adjunct to general anaesthesia, or sedation in the intensive care unit.

CONTRAINDICATIONS
Cisatracurium-AFT is contraindicated in patients known to be hypersensitive to cisatracurium besylate, atracurium or benzenesulfonic acid.

PRECAUTIONS
Cisatracurium besylate paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness or pain threshold. Cisatracurium-AFT 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 should be available.

Little information is available on the plasma levels and clinical consequences of cisatracurium metabolites that may accumulate during days to weeks of cisatracurium administration in ICU patients. Laudanosine, a major biologically active metabolite of atracurium and cisatracurium without neuromuscular blocking activity, produces transient hypotension and, in higher doses, cerebral excitatory effects (generalised muscle twitching and seizures) when administered to several species of animals. Consistent with the decreased infusion rate requirements of cisatracurium, plasma laudanosine concentrations are approximately one third those following atracurium infusion. There have been rare spontaneous reports of seizures in ICU patients who have received atracurium and other agents. These patients usually had predisposing causes (such as cranial trauma, cerebral oedema, hypoxic encephalopathy, viral encephalitis, uraemia). There are insufficient data to determine whether or not laudanosine contributes to seizures in ICU patients.

Caution should be exercised when administering Cisatracurium-AFT to patients who have shown allergic hypersensitivity to other neuromuscular blocking agents since a high rate of cross sensitivity (greater than 50%) between neuromuscular agents has been reported.

Cisatracurium besylate does not have significant vagolytic or ganglion blocking properties. Consequently, Cisatracurium-AFT 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 bodyweight cisatracurium besylate is recommended in these patients.

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 (see INTERACTIONS WITH OTHER MEDICINES).
Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking agents.

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

Patients with burns have been shown to develop resistance to non-depolarising neuromuscular blocking agents, including atracurium. The extent of altered response depends upon the size of the burn and the time elapsed since the burn injury. Cisatracurium has not been studied in patients with burns, however, based on its structural similarity to atracurium, the possibility of increased dosing requirements and shortened duration of action must be considered if Cisatracurium-AFT is administered to burn patients.

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

As with other drugs administered intravenously, when a small vein is selected as the injection site, Cisatracurium-AFT should be flushed through the vein with a suitable intravenous fluid (e.g. Sodium Chloride Intravenous Solution 0.9% w/v).

Cisatracurium-AFT does not contain an antimicrobial preservative. Dilution should, therefore, be carried out immediately prior to use. Administration should commence as soon as possible thereafter and any remaining solution should be discarded (see Instructions for use).

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

Enflurane or isoflurane anaesthesia may extend the clinically effective duration of an initial dose of Cisatracurium-AFT by as much as 15% in adults. In children, halothane may be expected to extend the clinically effective duration of a dose of Cisatracurium-AFT by up to 20%. No information is available on the use of Cisatracurium-AFT 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-AFT by up to 20%.

**Mutagenicity / Carcinogenicity**

Carcinogenesis and fertility studies have not been performed. Cisatracurium was evaluated for genotoxic potential in a battery of four tests. It was non-genotoxic in assays for clastogenic activity (in vitro human lymphocyte cytogenetics assay and a rat bone marrow cytogenetics assay) and an Ames Salmonella assay for gene mutations. As was the case with atracurium, the mouse lymphoma assay was positive.

**Use in Pregnancy**

Pregnancy Category: C

Teratology studies in non-ventilated pregnant rats treated subcutaneously with maximum subparalysing doses (4 mg/kg daily) and in ventilated rats treated intravenously with paralysing doses of cisatracurium (1.0 mg/kg), respectively, revealed no foetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of cisatracurium
in pregnant women. Because animal studies are not always predictive of human response, cisatracurium should be used during pregnancy only if clearly needed.

Doses of 0.2 or 0.4 mg/kg cisatracurium given to female beagles undergoing caesarean section resulted in negligible levels of cisatracurium in umbilical vessel blood of neonates and no deleterious effects on the puppies.

**Use in lactation**

Studies have not been conducted to determine whether cisatracurium or its metabolites are excreted in human or animal milk.

**Effects on laboratory tests**

None known

**INTERACTIONS WITH OTHER MEDICINES**

A number of drugs have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents.

The following drugs have been shown to increase the effects of non-depolarising neuromuscular blocking agents.

- **Anaesthetics:**
  - Volatile anaesthetics such as enflurane, isoflurane and halothane (see PRECAUTIONS).
  - Ketamine.
- **Other non-depolarising neuromuscular blocking agents.**
- **Antibiotics, including:**
  - the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin.
- **Anti-arrhythmic drugs, including:**
  - propanolol, calcium channel blockers, lignocaine, procainamide and quinidine.
- **Diuretics, including:**
  - frusemide and possibly thiazides, mannitol and acetazolamide.
- **Magnesium salts.**
- **Lithium salts.**
- **Ganglion blocking drugs (trimetaphan, hexamethonium).**

Prior chronic administration of phenytoin or carbamazepine has been shown to decrease the effects of non-depolarising neuromuscular blocking agents.

Prior 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 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 (propanolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), anti-rheumatic
drugs (chloroquine, 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.

ADVERSE REACTIONS

**Observed in clinical trials of surgical patients**

No adverse experiences considered to be reasonably attributable to cisatracurium were reported amongst 937 surgical patients studied during the clinical development programme. The following adverse experiences were judged by investigators during the clinical trials to have a possible causal relationship to administration of cisatracurium:

- **Incidence Greater than 1%:** None.
- **Incidence Less than 1%:**
  - Cardiovascular: Bradycardia (0.4%), hypotension (0.2%), flushing (0.2%).
  - Respiratory: Bronchospasm (0.2%).
  - Dermatological: Rash (0.1%).

**Observed in clinical trials of intensive care unit patients**

Three adverse experiences were reported among 68 ICU patients administered cisatracurium in conjunction with other drugs in clinical studies. One patient experienced bronchospasm, considered possibly attributable to cisatracurium. In one of the two ICU studies, a randomised and double-blind study of ICU patients using TOF neuromuscular monitoring, there were two reports of prolonged recovery (167 and 270 minutes) among 28 patients administered cisatracurium and 13 reports of prolonged recovery (range: 90 minutes to 33 hours) among 30 patients administered vecuronium.

**Observed During Clinical Practice**

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of cisatracurium besylate in conjunction with one or more anaesthetic agents in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to cisatracurium besylate.

**Hypersensitivity**

Very rarely: Severe anaphylactic reactions have been reported in patients receiving cisatracurium in conjunction with one or more anaesthetic agents.

Anaphylactic reactions of varying degrees of severity have been observed after the administration of neuromuscular blocking agents.

**Other reported reactions**

There have been some reports of muscle weakness and/or myopathy following prolonged use of muscle relaxants, including cisatracurium, in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids.
DOSAGE AND ADMINISTRATION

Cisatracurium-AFT contains no antimicrobial preservative and is intended for single use in one patient only.

Use by intravenous bolus injection

Dosage in Adults

Tracheal intubation

The recommended intubation dose of Cisatracurium-AFT for adults is 0.15 mg/kg bodyweight. 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 was administered at doses of 0.1 to 0.4 mg/kg bodyweight to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

<table>
<thead>
<tr>
<th>Initial cisatracurium dose (mg/kg body weight)</th>
<th>Anaesthetic background</th>
<th>Time to 90% T1* suppression (min)</th>
<th>Time to maximum T1* suppression (min)</th>
<th>Time to spontaneous T1* recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>Opioid</td>
<td>3.4</td>
<td>4.8</td>
<td>45</td>
</tr>
<tr>
<td>0.15</td>
<td>Propofol</td>
<td>2.6</td>
<td>3.5</td>
<td>55</td>
</tr>
<tr>
<td>0.2</td>
<td>Opioid</td>
<td>2.4</td>
<td>2.9</td>
<td>65</td>
</tr>
<tr>
<td>0.4</td>
<td>Opioid</td>
<td>1.5</td>
<td>1.9</td>
<td>91</td>
</tr>
</tbody>
</table>

* Single twitch response as well as the first component of the Train-of-Four response of the adductor pollicis muscle following the supramaximal electrical stimulation of the ulnar nerve

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

Maintenance

Neuromuscular block can be extended with maintenance doses of Cisatracurium-AFT. A dose of 0.03 mg/kg bodyweight 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 administered dose of Cisatracurium-AFT. 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 the administration of Cisatracurium-AFT is readily reversible with standard doses of anticholinesterase agents. Following the administration of the reversal agent at an average of 10% T1 recovery, 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.
Dosage in Paediatric Patients ages 1 month to 12 years

Tracheal Intubation

As in adults, the recommended intubation dose of Cisatracurium-AFT is 0.15 mg/kg bodyweight administered rapidly over 5 to 10 seconds. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection of Cisatracurium-AFT. 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 bodyweight may produce similar intubation conditions at 120 to 150 seconds.

In paediatric patients aged 1 month to 12 years, Cisatracurium-AFT has a shorter clinically effective duration and a faster spontaneous recovery profile than those observed with 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. Younger children (1 - 11 months old) demonstrated a longer mean clinical effective duration, as compared to the older children. However, there was no significant difference in the mean 25-75% recovery indices between the age groups.

<table>
<thead>
<tr>
<th>Paediatric Patients aged 1 to 11 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial cisatracurium dose (mg/kg bodyweight)</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>0.15</td>
</tr>
<tr>
<td>0.15</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Paediatric Patients aged 1 to 12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial cisatracurium dose (mg/kg bodyweight)</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>0.15</td>
</tr>
<tr>
<td>0.15</td>
</tr>
</tbody>
</table>

Data in the above tables are derived from Study 139-027, an open-label study in ASA I/II paediatric patients aged 1 month to 12 years. For data presented, patients were randomised to N₂O/O₂/halothane (n=90) or N₂O/O₂/opioid (n=89) anaesthesia. Within each anaesthetic group patients were stratified into three age groups; 1-11 months, 12-59 months or 60-155 months. Neuromuscular blocking profile was assessed at the adductor pollicis by electromyography.

When Cisatracurium-AFT 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:
### Initial cisatracurium dose (mg/kg bodyweight) | Number of patients studied | Anaesthetic background | Time to 90% suppression (min) | Time to maximum suppression (min) | Time to 25% spontaneous $T_1$ recovery (min)
---|---|---|---|---|---
0.08 | 32 | Halothane | 1.7 | 2.5 | 31
0.1 | 16 | Opioid | 1.7 | 2.8 | 28

Data in the above table are derived from an open-label study in ASA I/II paediatric patients aged 2-12 years. Neuromuscular block was assessed at the adductor pollicis by electromyography.

Halothane may be expected to extend the clinically effective duration of a dose of Cisatracurium-AFT by up to 20%. No information is available on the use of Cisatracurium-AFT 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-AFT by up to 20%.

**Maintenance**
Neuromuscular block can be extended with maintenance doses of Cisatracurium-AFT. A dose of 0.02 mg/kg bodyweight 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**
During opioid anaesthesia the median times from 25 to 75% and from 5 to 95% recovery are approximately 10 and 25 minutes respectively.

**Reversal**
Neuromuscular block following the administration of Cisatracurium-AFT is readily reversible with standard doses of anticholinesterase agents. Following the administration of the reversal agent at an average of 13% $T_1$ recovery, 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.

**Use by intravenous infusion**

**Dosage in Adults and Paediatric Patients aged 1 month to 12 years**
Maintenance of neuromuscular block may be achieved by infusion of Cisatracurium-AFT. An initial infusion rate of 3 $\mu$g/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 $\mu$g/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-AFT is administered during isoflurane or enflurane anaesthesia (see INTERACTIONS WITH OTHER MEDICINES).

The infusion rate will depend upon the concentration of cisatracurium besylate in the infusion solution, the desired degree of neuromuscular block and the patient’s weight. The following table provides guidance for delivery of undiluted Cisatracurium-AFT 2 mg/mL.
Continuous infusion of Cisatracurium-AFT is not associated with a progressive increase or decrease in neuromuscular blocking effect.

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

**Dosage in neonates aged less than 1 month**
No dosage recommendation for neonates can be made as administration of cisatracurium has not been studied in this patient population.

**Dosage in Intensive Care Unit (ICU) patients**
Cisatracurium-AFT may be administered by bolus dose and/or infusion to adult patients in the ICU.

An initial infusion rate of Cisatracurium-AFT 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/min (range 0.5 to 10.2 μg/kg/min or 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 in ICU patients was approximately 50 minutes.

**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, however 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.

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 (8 x ED₉₅)).

Dosage in patients undergoing hypothermic cardiac surgery
There have been no studies of Cisatracurium-AFT 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.

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

Instructions for use
Physical Compatibilities
Diluted Cisatracurium-AFT is chemically and physically stable for at least 12 hours, when stored in either polyvinyl chloride or polypropylene containers, at concentrations between 0.1 and 2.0 mg/mL in the following infusion solutions:
- 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
The product contains no antimicrobial preservative and therefore should be used immediately on dilution, or failing this should be stored at 2 to 8°C for no more than 24 hours, after which time unused solution should be discarded. Dilution should, therefore, be carried out immediately prior to use. Administration should commence as soon as possible thereafter and any remaining solution should be discarded. Containers of Cisatracurium-AFT and any syringe containing Cisatracurium-AFT are for single use in individual patients. At the end of the procedure or at 24 hours following preparation, whichever is the sooner, both the reservoir of Cisatracurium-AFT and the infusion line must be discarded and replaced as appropriate.

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
Where other drugs are administered through the same indwelling needle or cannula as Cisatracurium-AFT, 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).

**Physical Incompatibilities**
Cisatracurium-AFT is not chemically stable when diluted in Lactated Ringer's Injection.

Since Cisatracurium-AFT 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. thiopentone). Cisatracurium-AFT is not compatible with ketorolac, trometamol or propofol injection emulsion.

**OVERDOSAGE**

**Symptoms and signs**
Prolonged muscle paralysis and its consequences are expected to be the main signs of overdose with Cisatracurium-AFT.

**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-AFT. Recovery may be accelerated by the administration of anticholinesterase agents once evidence of spontaneous recovery is present.

**PRESENTATION AND STORAGE CONDITIONS**
Cisatracurium-AFT is a colourless to pale yellow or greenish yellow solution. It is available in the following strengths and pack sizes:

- 5 mg/2.5 mL: packs of 1 or 5 ampoules: AUST R 191832
- 10 mg/5 mL: packs of 1 or 5 ampoules: AUST R 191831
- 20 mg/10 mL: packs of 1 or 5 ampoules: AUST R 191833
- 150 mg/30 mL: packs of 1 vial: AUST R 191834

Cisatracurium-AFT should be stored between 2° and 8°C. Refrigerate. Do not freeze. Protect from light.

**NAME AND ADDRESS OF THE SPONSOR**

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**New Zealand**
AFT Pharmaceuticals Ltd
Auckland
POISON SCHEDULE OF THE MEDICINE
S4
Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG
25 January 2013

DATE OF THIS AMENDMENT
12 December 2013