**DESCRIPTION:**

Cisatracurium Besylate Injection is a nondepolarizing skeletal muscle relaxant for intravenous administration. Compared to other neuromuscular blocking agents, it is intermediate in its onset and duration of action. Cisatracurium besylate is one of 10 isomers of atracurium besylate and constitutes approximately 15% of that mixture. Cisatracurium besylate is \( [1R-1α,2α(1*R*,2*R*)]-2,2-\{1,5-pentanediylybis[oxy]3-oxet-3-1-propanediyl|]] \) bis\([1\{2,3,4,4-tetrahydropyridin-3-yly]|2,2\) dibenzenesulfonate. The molecular formula of the cisatracurium parent bis-cation is \( \text{C}_{50}\text{H}_{92}\text{O}_{39}\text{S}_{22} \) and the molecular weight is 929.2. The molecular formula of cisatracurium as the besylate salt is \( \text{C}_{69}\text{H}_{108}\text{O}_{40}\text{S}_{22}\) and the molecular weight is 1343.50.

The structural formula of cisatracurium besylate is:

![Structural formula of cisatracurium besylate](image)

The log of the partition coefficient of cisatracurium besylate is -2.12 in a 1-octanol/distilled water system at 25°C. Cisatracurium Besylate Injection is a sterile, non-pyrogenic aqueous solution provided in 5 mL, 10 mL, and 20 mL vials. The pH is adjusted to 3.25 to 3.65 with 1.23.4-tetrahydro-6,7-dimethoxy-2-methylisouquinolinium dibenzenesulfonate. The molecular formula of the cisatracurium parent bis-cation is \( \text{C}_{50}\text{H}_{92}\text{O}_{39}\text{S}_{22} \) and the molecular weight is 929.2. The molecular formula of cisatracurium as the besylate salt is \( \text{C}_{69}\text{H}_{108}\text{O}_{40}\text{S}_{22}\) and the molecular weight is 1343.50.

**NOT FOR USE IN NEONATES**

CONTAINS BENZYL ALCOHOL

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

---

**Pharmacodynamics**

The neuromuscular blocking potency of cisatracurium is approximately threefold that of atracurium besylate. The time to maximum block is up to 2 minutes longer for equipotent doses of cisatracurium compared to atracurium besylate. The clinically effective duration of action and rate of spontaneous recovery from equipotent doses of cisatracurium and atracurium besylate are similar.

The average ED<sub>95</sub> (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of cisatracurium is 0.05 mg/kg (range: 0.048 to 0.053) in adults receiving opioid/nitrous oxide/oxygen anesthesia. For comparison, the average ED<sub>95</sub> for atracurium when also expressed as the parent bis-cation is 0.17 mg/kg under similar anesthetic conditions.

The pharmacodynamics of 2 x ED<sub>95</sub> to 8 x ED<sub>95</sub> doses of cisatracurium administered over 5 to 10 seconds during opioid/nitrous oxide/oxygen anesthesia are summarized in Table 1. When the dose is doubled, the clinically effective duration of block increases by approximately 25 minutes. Once recovery begins, the rate of recovery is independent of dose.

Isoflurane or enflurane administered with nitrous oxide/oxygen to achieve 1.25 MAC [Minimum Alveolar Concentration] may prolong the clinically effective duration of action of initial and maintenance doses, and decrease the average infusion rate requirement of cisatracurium. The magnitude of these effects may depend on the duration of administration of the volatile agents. Fifteen to 30 minutes of exposure to 1.25 MAC isoflurane or enflurane had minimal effects on the duration of action of initial doses of cisatracurium and therefore, no adjustment to the initial dose should be necessary when cisatracurium is administered shortly after initiation of volatile agents. In long surgical procedures during enflurane or isoflurane anesthesia, less frequent maintenance dosing, lower maintenance doses, or reduced infusion rates of cisatracurium may be necessary. The average infusion rate requirement may be decreased by as much as 30% to 40%.

The onset, duration of action, and recovery profiles of cisatracurium during propofol/oxygen or propofol/nitrous oxide/oxygen anesthesia are similar to those during opioid/nitrous oxide/oxygen anesthesia.
This drug should be administered only by adequately trained personnel.

Cisatracurium Besylate is 1243.50.

The neuromuscular blocking potency of cisatracurium compared to atracurium when also expressed as the par-5 ratio is 12 to 15.

While GOOD or EXCELLENT intubation conditions were achieved in the majority of patients in this setting, EXCELLENT intubation conditions were more frequently achieved with the 0.2 mg/kg dose when intubation was attempted 1.5 minutes following cisatracurium administration. A second study evaluated intubation conditions after 3 and 4 x ED95 (0.15 mg/kg and 0.2 mg/kg) following induction with fentanyl and midazolam and either thiopental or propofol anesthesia. This study compared intubation conditions produced by these doses of cisatracurium after 1.5 minutes. Table 3 displays these results.

Table 3. Study of Tracheal Intubation Comparing Three Doses of Cisatracurium (Thiopental or Propofol Anesthesia) (Cont'd.)

<table>
<thead>
<tr>
<th>Intubating Conditions at 90 seconds</th>
<th>3 x ED95 0.15 mg/kg n = 21</th>
<th>4 x ED95 0.2 mg/kg n = 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>2/23 (13%)</td>
<td>2/23 (13%)</td>
</tr>
<tr>
<td>Good</td>
<td>15/26 (70%)</td>
<td>20/23 (87%)</td>
</tr>
</tbody>
</table>

EXCELLENT intubation conditions were more frequently observed with the 0.2 mg/kg dose when intubation was attempted 1.5 minutes following cisatracurium.

A third study in pediatric patients (ages 1 month to 12 years) evaluated intubation conditions at 120 seconds after 0.15 mg/kg cisatracurium following induction with either halothane (with halothane/nitrous oxide/oxygen maintenance) or thiopental and fentanyl (with thiopen/talent/nitrous oxide/oxygen maintenance). The results are summarized in Table 4.

Table 4. Study of Tracheal Intubation for Pediatrics Stratified by Age Group (0.15 mg/kg Cisatracurium with Halothane or Thiopental/Fentanyl Anesthesia)

<table>
<thead>
<tr>
<th>Intubating Conditions at 120 seconds**</th>
<th>Cisatracurium 0.15 mg/kg 1 to 11 mo. n = 30</th>
<th>Cisatracurium 0.15 mg/kg 1 to 4 years n = 30</th>
<th>Cisatracurium 0.15 mg/kg 5 to 12 years n = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent or Good</td>
<td>29/30 (97%)</td>
<td>29/30 (97%)</td>
<td>29/30 (97%)</td>
</tr>
<tr>
<td>%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Percent</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Excellent</td>
<td>28/30 (93%)</td>
<td>27/30 (90%)</td>
<td>26/30 (87%)</td>
</tr>
<tr>
<td>%</td>
<td>93%</td>
<td>90%</td>
<td>87%</td>
</tr>
<tr>
<td>Percent</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Good</td>
<td>6/30 (93%)</td>
<td>5/30 (83%)</td>
<td>5/30 (83%)</td>
</tr>
<tr>
<td>%</td>
<td>20%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Percent</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
</tbody>
</table>

EXCELLENT or GOOD intubating conditions were produced 120 seconds following 0.15 mg/kg cisatracurium in 88/90 (98%) of patients induced with halothane and in 85/90 (94%) of patients induced with thiopental and fentanyl. There were no patients for whom intubation was not possible, but there were 7/120 patients ages 1 to 12 years for whom intubating conditions were described as poor. Repeated administration of maintenance doses or a continuous infusion of cisatracurium for up to 3 hours is not associated with development of tachyphylaxis or cumulative neuromuscular blocking effects. The time needed to recover from successive maintenance doses does not change with the number of doses administered as long as partial recovery is allowed to occur between doses. Maintenance doses can be administered at relatively regular intervals with predictable results. The rate of spontaneous recovery of neuromuscular function after infusion is independent of the duration of intubation and comparable to the rate of recovery following initial doses (Table 1).

Long-term infusion (up to 6 days) of cisatracurium during mechanical ventilation in the ICU has been evaluated in two studies. In a randomized, double-blind study using presence of a single twitch during train-of-four (TOF) monitoring to regulate dosage, patients treated with cisatracurium (n = 101) recovered neuromuscular function (T1/T0 ratio ≥ 70%) following termination of infusion in approximately 55 minutes (range: 20 to 270) whereas those treated with vecuronium (n = 12) recovered in 178 minutes (range: 40 minutes to 33 hours). In another study comparing cisatracurium and atracurium, patients recovered neuromuscular function in approximately 50 minutes for both cisatracurium (range: 20 to 175; n = 34) and atracurium (n = 35).

The neuromuscular block produced by cisatracurium is readily antagonized by anticholinesterase agents once recovery has started. As with other non-depolarizing neuromuscular blocking agents, the more profound the neuromuscular block at the time of reversal, the longer the time required for recovery of neuromuscular function. In children (2 to 12 years) cisatracurium has a lower ED95 than in adults (0.04 mg/kg/hr). The ratio of ED50 and ED95 for atracurium when also expressed as the par-5 ratio is 12 to 15. The neuromuscular block produced by cisatracurium is readily antagonized by anticholinesterase agents once recovery has started. As with other non-depolarizing neuromuscular blocking agents, the more profound the neuromuscular block at the time of reversal, the longer the time required for recovery of neuromuscular function. In children (2 to 12 years) cisatracurium has a lower ED95 than in adults (0.04 mg/kg/hr). The ratio of ED50 and ED95 for atracurium when also expressed as the par-5 ratio is 12 to 15.
A total of 141 patients undergoing coronary artery bypass grafting (CABG) have been administered cisatracurium in three active controlled clinical trials and have received doses ranging from 2 to 8 x ED₉₀. While the hemodynamic profile was comparable in both the cisatracurium and active control groups, data for doses above 0.3 mg/kg in this population are limited.

Unlike atracurium, cisatracurium, at therapeutic doses of 2 x ED₉₀ to 8 x ED₉₀ (0.1 to 0.4 mg/kg), administered over 5 to 10 seconds, does not cause dose-related elevations in mean plasma histamine concentration.

![Figure 1. Maximum Percent Change from Preinjection in Heart Rate (HR) and Mean Arterial Pressure (MAP) During First 5 Minutes after Initial 4 x ED₉₀ to 8 x ED₉₀ Doses of Cisatracurium in Healthy Adult Patients Receiving Opioid/Nitrous Oxide/Oxygen Anesthesia (n = 44)](image)

![Figure 2. Percent Change from Preinjection in Heart Rate (HR) and Mean Arterial Pressure (MAP) 10 Minutes After Initial 4 x ED₉₀ to 8 x ED₉₀ Doses of Cisatracurium in Patients Undergoing CABG Surgery Receiving Oxygen/Fentanyl/Midazolam/Anesthesia (n = 54)](image)

No clinically significant changes in MAP or HR were observed following administration of doses up to 0.1 mg/kg cisatracurium over 5 to 10 seconds in 2- to 12-year-old children receiving either halothane/nitrous oxide/oxygen or opioid/nitrous oxide/oxygen anesthesia. Doses of 0.15 mg/kg cisatracurium administered over 5 seconds were not consistently associated with changes in HR and MAP in pediatric patients aged 1 month to 12 years receiving opioid/nitrous oxide/oxygen/nitrous oxide/oxygen anesthesia.

![Figure 3. Heart Rate and MAP Change at 1 Minute After the Initial Dose. By Age Group Treatment Group: Cisatracurium 0.3 x ED₉₀ Intubation 120 Sec. 1 to 11 Months)](image)

No clinically significant changes in MAP or HR were observed following administration of doses up to 0.1 mg/kg cisatracurium over 5 to 10 seconds in 2- to 12-year-old children receiving either halothane/nitrous oxide/oxygen or opioid/nitrous oxide/oxygen anesthesia. Doses of 0.15 mg/kg cisatracurium administered over 5 seconds were not consistently associated with changes in HR and MAP in pediatric patients aged 1 month to 12 years receiving opioid/nitrous oxide/oxygen/nitrous oxide/oxygen anesthesia.

![Figure 4. Heart Rate and MAP Change at 1 Minute After the Initial Dose. By Age Group Treatment Group: Cisatracurium H:3 x ED₉₀ Halothane Intubation 120 Sec. 1 to 11 Months)](image)

### Pharmacokinetics

#### General

The neuromuscular blocking activity of cisatracurium is due to parent drug. Cisatracurium plasma concentration-time data following IV bolus administration are best described by a two-compartment open model (with elimination from both compartments) with an elimination half-life (t½) of 22 minutes, a plasma clearance (CL) of 4.57 ± 0.5 mL/min/kg, and a volume of distribution at steady state (Vss) of 1.45 ± 0.4 mL/kg. Cisatracurium undergoes organ-independent Hofmann elimination (a chemical process dependent on pH and temperature) to form the monooxynacrylacetate metabolite and laudanosine, neither of which has any neuromuscular blocking activity (see Pharmacokinetics, Metabolism). Following administration of radiolabeled cisatracurium, 95% of the dose was recovered in the urine; less than 10% of the dose was excreted as unchanged parent drug. Laudanosine, a metabolite of cisatracurium (and atracurium) has been noted to cause transient hypotension and, in higher doses, cerebral excitatory effects which were associated with several animal species. The relationship between CNS excitation and laudanosine concentrations in humans has not been established (see PRECAUTIONS, Long-Term Use in the Intensive Care Unit (ICU)).

Cisatracurium is a three times more potent than atracurium. AUC values are required, the corresponding laudanosine concentrations following cisatracurium are one third of that would be expected following an equipotent dose of atracurium (see Pharmacokinetics, Special Populations, Intensive Care Unit Patients).

Results from population pharmacokinetic/pharmacodynamic (PK/PD) analyses from 241 healthy surgical patients are summarized in Table 5.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate¹</th>
<th>Magnitude of Interpatient Variability (CV)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>V₅₀ (mL/kg)</td>
<td>4.57</td>
<td>16%</td>
</tr>
<tr>
<td>K₉₀ (min⁻¹)</td>
<td>1.2</td>
<td>27%</td>
</tr>
<tr>
<td>EDC₀ (mg/kg)</td>
<td>0.00575</td>
<td>61%</td>
</tr>
<tr>
<td>* Values presented are mean ± SD.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Healthy male non-obese patients 19 to 64 years of age with creatinine clearance values greater than 70 mL/min who received cisatracurium during opioid anesthesia and venous samples collected.*

The percent standard error of the mean (SEM) ranged from 3% to 12% indicating good precision for the PK/PD estimates. Expressed as a coefficient of variation, the SEM ranged from 20% to 35% indicating adequate precision for the estimates of interpatient variability.

V₅₀ is the volume of distribution at steady state estimated using a two-compartment model with elimination from both compartments. V₅₀ is equal to the sum of the volume in the central compartment (V₁) and the volume in the peripheral compartment (V₂). Interpatient variability could only be estimated for V₂.

Rate constant describing the equilibration between plasma concentrations and neuromuscular block.

*Concentration required to produce 50% T₁ suppression; an index of patient sensitivity.

The magnitude of interpatient variability in CL was low (16%), as expected based on the importance of Hofmann elimination (see Pharmacokinetics, Elimination). The magnitude of interpatient variability in CL and volume of distribution were low in comparison to those for K₉₀ and V₅₀. This suggests that any alteration in the time course of cisatracurium-induced block are more likely to be due to variability in the pharmacodynamic parameters than in the pharmacokinetic parameters. Parameter estimates from the population pharmacokinetic analyses were supported by noncompartmental pharmacokinetic analyses on data from healthy patients and from special patient populations.

Conventional pharmacokinetic analyses have shown that the pharmacokinetics of cisatracurium are proportional to dose between 0.1 (2 x ED₉₀) and 0.4 (4 x ED₉₀) mg/kg cisatracurium. In addition, population pharmacokinetic analyses revealed no statistically significant effect of initial dose on CL for doses between 0.1 (2 x ED₉₀) and 0.4 (4 x ED₉₀) mg/kg cisatracurium.

#### Distribution

The volume of distribution of cisatracurium is limited by its large molecular weight and high polarity. The CL₉₀ was equal to 145 mL/kg (Table 4) in healthy 19- to 64-year-old surgical patients receiving inhalation anesthesia. The V₅₀ was 21% larger in similar patients receiving inhalation anesthesia (see Pharmacokinetics, Special Populations, Other Patient Factors).

#### Protein Binding

The binding of cisatracurium to plasma proteins has not been successfully studied due to its rapid degradation at physiological pH. Inhibition of degradation requires non-physiological conditions of temperature and pH which are associated with changes in protein binding.

#### Metabolism

The degradation of cisatracurium is largely independent of liver metabolism. Results from in vitro experiments suggest that cisatracurium undergoes Hofmann elimination (a pH and temperature-dependent chemical process) to form laudanosine (see PRECAUTIONS, Long-Term Use in the Intensive Care Unit (ICU)) and the monooxyacrylacetate metabolite. The monooxyacrylacetate undergos hydrolysis by non-specific esterases to form the monoquinoxaline alcohol (MQA) metabolite. The MQA metabolite can also undergo Hofmann elimination but at a much slower rate than cisatracurium. Laudanosine is further metabolized to desmethyl metabolites which are conjugated with glucuronic acid and excreted in the urine.

Organ-independent Hofmann elimination is the predominant pathway for the elimination of cisatracurium. The liver and kidney play a minor role in the elimination of cisatracurium but are primary pathways for the elimination of metabolites. Therefore, the (β values of metabolites (including laudanosine) are lower in patients with kidney or liver dysfunction and metabolite concentrations may be higher after long-term administration (see PRECAUTIONS, Long-Term Use in the Intensive Care Unit (ICU)).

#### Elimination

Clearance and Half-Life

Table 5. Key Population PK/PD Parameter Estimates for Cisatracurium in Healthy Surgical Patients* Following 0.1 (2 x ED₉₀) to 0.4 mg/kg (8 x ED₉₀) Cisatracurium

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate¹</th>
<th>Magnitude of Interpatient Variability (CV)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (mL/min/kg)</td>
<td>4.57</td>
<td>16%</td>
</tr>
<tr>
<td>V₅₀ (mL/kg)</td>
<td>1.2</td>
<td>27%</td>
</tr>
<tr>
<td>K₉₀ (min⁻¹)</td>
<td>0.0575</td>
<td>61%</td>
</tr>
<tr>
<td>EDC₀ (mg/kg)</td>
<td>145</td>
<td>52%</td>
</tr>
</tbody>
</table>

* Values presented are mean ± SD.

Mean CL values for cisatracurium ranged from 4.5 to 5.7 mL/min/kg in studies of healthy surgical patients. Conventional pharmacokinetic modeling suggests that approximately 86% of the CL is accounted for by Hofmann elimination and the remaining 20% by renal and hepatic elimination. These findings are consistent with the low magnitude of interpatient variability in CL (16%) estimated as part of the population PK/PD analyses and with the recovery of parent and metabolites in urine. Fol-
Patients with Renal Dysfunction

Results from a conventional pharmacokinetic study of cisatracurium in 13 healthy adult patients and 15 patients with renal failure (estimated GFR [eGFR] < 60 mL/min [45 mL/min] per 1.73 m²) undergoing elective surgery are summarized in Table 8. The PK/PD parameters of cisatracurium were similar in healthy adult patients and patients with renal failure. However, even times to 95% block were approximately one minute slower in eGFR patients following 0.1 mg/kg cisatracurium. There were no differences in 4:T1 or ratios of recovery of cisatracurium between eGFR and healthy adult patients. 

The Table 8. Pharmacokinetic Parameters* for Cisatracurium in Healthy Adult Patients and in Patients With End-Stage Renal Disease (ESRD) Receiving a 0.15 mg/kg Cisatracurium (Opioid/Nitrous Oxide/Oxygen Anesthesia)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cisatracurium (n = 6)</th>
<th>ESRD Patients (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination Half-Life (hrs)</td>
<td>8.4 ± 3.9</td>
<td>22.6 ± 10.3</td>
</tr>
<tr>
<td>Volume Distribution of Cisatracurium (ml/kg)</td>
<td>27.1 ± 8.3</td>
<td>20.7 ± 9.1</td>
</tr>
<tr>
<td>Plasma Clearance (ml/min)</td>
<td>4.6 ± 0.8</td>
<td>4.2 ± 0.6</td>
</tr>
</tbody>
</table>

*Values presented are mean ± SD.

Population pharmacokinetic analyses revealed that patients with creatinine clearances ≤ 70 mL/min had a slower rate of equilibration between plasma concentrations and neuromuscular block than patients with normal renal function; this change was associated with a slightly longer (−40%) and a 20% to 30% 1 suppression in patients with renal dysfunction following 0.1 mg/kg cisatracurium. There was no clinically significant alteration in the recovery profile of cisatracurium in patients with renal dysfunction. The recovery profile of cisatracurium is unchanged in the presence of renal and hepatic failure which is consistent with predominantly organ-independent elimination.

Intensive Care Unit (ICU) Patients

The pharmacokinetics of cisatracurium, atracurium, and their metabolites were determined in six ICU patients receiving cisatracurium and atracurium. The results are presented in Table 9. The plasma clearances of cisatracurium and atracurium are similar. The volume of distribution was larger and the t½ was longer for cisatracurium than for atracurium. The relationships between plasma cisatracurium or atracurium concentrations and neuromuscular block have not been evaluated in ICU patients. The minor differences in pharmacokinetics were not associated with any differences in the recovery profiles of cisatracurium and atracurium in ICU patients.

Table 9. Parameter Estimates* for Cisatracurium, Atracurium, and Metabolites in ICU Patients After Long-Term (24 to 48 Hour) Administration of Cisatracurium or Atracurium Besylate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cisatracurium (n = 6)</th>
<th>Atracurium (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>Compound</td>
<td>CL (ml/min)</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>C80</td>
<td>10.4 ± 3.6</td>
</tr>
<tr>
<td></td>
<td>C100</td>
<td>11.9 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>C50</td>
<td>7.8 ± 4.1</td>
</tr>
<tr>
<td></td>
<td>C25</td>
<td>4.9 ± 4.1</td>
</tr>
<tr>
<td></td>
<td>C125</td>
<td>131 ± 35</td>
</tr>
</tbody>
</table>

* Values presented as mean ± standard deviation.

Volume of distribution during the terminal elimination phase, an underestimate because elimination from the peripheral compartment is ignored.

Intensive Care Unit (ICU) Patients

The pharmacokinetics of cisatracurium, atracurium, and their metabolites were determined in six ICU patients receiving cisatracurium and atracurium. The results are presented in Table 9. The plasma clearances of cisatracurium and atracurium are similar. The volume of distribution was larger and the t½ was longer for cisatracurium than for atracurium. The relationships between plasma cisatracurium or atracurium concentrations and neuromuscular block have not been evaluated in ICU patients. The minor differences in pharmacokinetics were not associated with any differences in the recovery profiles of cisatracurium and atracurium in ICU patients.

Contraindications

Cisatracurium is contraindicated in patients with known hypersensitivity to the product or its components. Cisatracurium should not be administered with other neuromuscular blocking agents or to patients who are receiving other neuromuscular blocking agents since cross-reactivity between neuromuscular blocking agents, both depolarizing and non-depolarizing, has been reported in this class of drugs. Administration

CISATRACURIUM SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG’S ACTIONS AND THE POSSIBLE

Pharmacokinetic Parameters* of Cisatracurium in Healthy Elderly and Young Adult Patients (0.1 mg/kg Cisatracurium (Isoflurane/Nitrous Oxide/Oxygen Anesthesia)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Elderly Patients (n = 23)</th>
<th>Healthy Young Adult Patients (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination Half-Life (hrs)</td>
<td>7.3 ± 3.6</td>
<td>6.2 ± 3.5</td>
</tr>
<tr>
<td>Volume Distribution of Cisatracurium (ml/kg)</td>
<td>25 ± 7.9</td>
<td>26 ± 7.9</td>
</tr>
<tr>
<td>Plasma Clearance (ml/min)</td>
<td>5.3 ± 0.9</td>
<td>5.3 ± 0.9</td>
</tr>
</tbody>
</table>

*Values presented are mean ± SD.

Population pharmacokinetic analyses revealed that there were no statistically significant differences in the parameters ratios in elderly and young adult patients.

Thiopentone and Fentanyl (Women)

The mean time to onset of maximum T1:T0 ratio of thiopentone was 3.6 ± 2.4 minutes. The mean time to onset of maximum T1:T0 ratio of fentanyl was 1.9 ± 1.1 minutes. There were no statistically significant differences in the parameters between women and men.

Table 7. Pharmacokinetic Parameters* of Cisatracurium in Healthy Surgical Populations (0.15 mg/kg Cisatracurium with Halothane Anesthesia)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cisatracurium (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination Half-Life (hrs)</td>
<td>8.4 ± 3.9</td>
</tr>
<tr>
<td>Volume Distribution (ml/kg)</td>
<td>27.1 ± 8.3</td>
</tr>
<tr>
<td>Plasma Clearance (ml/min)</td>
<td>4.6 ± 0.8</td>
</tr>
</tbody>
</table>

*Values presented are mean ± SD.

Burns

Patients with burns have been shown to develop resistance to nondepolarizing neuromuscular blocking agents, and may require individualization of dosing (see PRECAUTIONS).

Pediatric Patients

The population PK/PD of cisatracurium were described in 20 healthy pediatric patients during halothane anesthesia using the same model for adult patients. The CL was higher in healthy pediatric patients (5.89 mL/min/kg) than in healthy adult patients (4.13 mL/min/kg) during anesthesia. The rate of equilibration between plasma concentrations and neuromuscular block, as indicated by kapp, was faster in healthy pediatric patients receiving 0.17 mg/kg cisatracurium (45 minutes) than in healthy adult patients receiving opioid anesthesia (0.50 mg/kg cisatracurium (75 minutes)). The infusion rate requirement may be higher in patients with renal failure and concentrations may be higher after long-term administration (see Pharmacokinetics, Special Populations, Intensive Care Unit Patients). The minor differences in pharmacokinetics were not associated with any differences in the recovery profiles of cisatracurium and atracurium in young adult patients.

Thiopentone and Fentanyl (Men)

The mean time to onset of maximum T1:T0 ratio of thiopentone was 3.5 ± 2.4 minutes. The mean time to onset of maximum T1:T0 ratio of fentanyl was 1.9 ± 1.1 minutes. There were no statistically significant differences in the parameters between men and women.
COMPLICATIONS OF ITS USE. IT IS RECOMMENDED NOT TO MEASURE NEUROMUSCULAR FUNCTION DURING THE ADMINISTRATION OF CISATRACURUM IN ORDER TO MONITOR DRUG EFFECT. TRACHEAL INTUBATION, ADDITIONAL DOSES, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

CISATRACURUM HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRAVATION. TO AVOID THE RISK OF POSITIVE AIRWAY PRESSURE IN NEONATES, A BIOLOGICALLY ACTIVE METABOLITE OF ATRACURIUM AND CISATRACURUM IS NOT KNOWN. PREPARATIONS IN WHICH PROPORTIONED NEUROMUSCULAR BLOCK IS RECOMMENDED.

Pediatric Use (see WARNINGS for these combined sources. Single use vials (5 mL and 20 mL) of cisatracurium do not contain benzyl alcohol (see Contraindications and PRECAUTIONS, Pediatric Use).

PRECAUTIONS:

Because of its intermediate onset of action, cisatracurium is not recommended for rapid sequence endotracheal intubation. Recommended doses of cisatracurium have no clinically significant effects on heart rate; therefore, cisatracurium may be used in patients with the morbid cardiopulmonary reserve or in many anesthetic agents or by vagal stimulation.

Neuromuscular blocking drugs have a profound effect in patients with neuromuscular diseases (e.g., myasthenia gravis and the myasthenic syndrome). In these patients, the degree of depression of neuromuscular block is a possibility (e.g., carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.02 mg/kg cisatracurium is recommended to assess the level of neuromuscular block and to monitor dosage requirements. Patients with myasthenia gravis have been shown to develop resistance to non-depolarizing neuromuscular blocking agents, including cisatracurium. The intensity of this resistance is dose-dependent upon the size of the burn and the time elapsed since the burn injury. Cisatracurium has not been studied in patients with thermal injury who required the use of ventilator settings due to the possibility of increased dosing and shortened duration of action must be considered and the clinical status of the burn patients.

Patients with hemiparesis or paraparesis also may demonstrate resistance to non-depolarizing muscle relaxants in the affected limbs. To avoid inaccurate dosing, neuromuscular monitoring should be performed on a non-paralytic limb. Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. No data are available to support the use of cisatracurium by intramuscular injection.

Bacterial Infection

Since allergic cross-reactivity has been reported in this class, request information from your patients about previous allergic reactions to cisatracurium or other neuromuscular blocking agents. In addition, inform your patients that severe anaphylactic reactions to neuromuscular blocking agents, including cisatracurium have been reported (see CONTRAINDICATIONS).

Renal and Hepatic Disease

No information is available in the recovery profile were observed in patients with renal dysfunction or in patients with end-stage liver disease following a 0.1 mg/kg dose of cisatracurium. The average duration of action was approximately 1 minute faster in patients with end-stage liver disease and approximately 1 minute slower in patients with renal dysfunction compared to their healthy adult control patients.

Malignant Hyperthermia (MH)

In a study of MH-susceptible pigs, cisatracurium besylate (highest dose 2000 mcg/kg; equivalent to 3 ED90 in pigs and 4 ED90 in humans) did not trigger the MH response. Cisatracurium besylate has not been studied in MH-susceptible patients. MH can occur in the presence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU)

Long-term infusion (up to 6 days) of cisatracurium during mechanical ventilation in the ICU has been safely used in two studies. The minimum amount of benzyl alcohol at which toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flushed solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative may increase the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than one high dosage of medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources. Single use vials (5 mL and 20 mL) of cisatracurium do not contain benzyl alcohol (see Contraindications and PRECAUTIONS, Pediatric Use).

NOTE:

Parameters for the use of cisatracurium during labor, vaginal delivery, induction of anesthesia. When administered during stable opioid/nitrous oxide/oxygen induction-intubation technique. If the principles for infusion of cisatracurium in the OR were followed, termination of infusion in approximately 55 minutes (range: 20 to 270) whereas evaluable vornumetum-treated patients required approximately 26 minutes (range: 40 minutes to 33 hours). In another study comparing cisatracurium and atracurium, patients received neuromuscular function meanwhile for 5 minutes for both (range: 20 to 175; n = 34) and atracurium range: 35 to 60 minutes). When the use of cisatracurium is continued beyond 4 hours (see Pharmacokinetics, Special Populations, Intensive Care Unit Patients).

In a randomized, double-blind study using 164 mg of four nerve stimulator to maintain at least one visible evoked, patients treated with cisatracurium (n = 19) recovered neuromuscular function (T1-T1 ratio ≥ 70) following termination of infusion in approximately 55 minutes (range: 20 to 270) whereas evaluable venumetum-treated patients required approximately 26 minutes (range: 40 minutes to 33 hours). In another study comparing cisatracurium and atracurium, patients received neuromuscular function meanwhile for 5 minutes for both (range: 20 to 175; n = 34) and atracurium range: 35 to 60 minutes). When the use of cisatracurium is continued beyond 4 hours (see Pharmacokinetics, Special Populations, Intensive Care Unit Patients).

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COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT

must take into account the total amount of benzyl alcohol

The amount of benzyl alcohol from medications is usually

with exposure to excessive amounts of benzyl alcohol.

more than 0.02 mg/kg cisatracurium is recommended to

blocking agents. No data are available to support the use

Neuromuscular blocking agents may have a profound

INFUSION ADMINISTRATION SHOULD BE DISCONTINUED

NEUROMUSCULAR BLOCKING AGENT SHOULD NOT

sides, tetracyclines, bacitracin, polymyxins, lincomycin,

blocking action of non-depolarizing agents such as cisa-

isoflurane anesthesia, less frequent maintenance dosing,

to the initial dose should be necessary when cisatra-

intubating dose of succinylcholine (1 mg/kg) produced

hours (see

Resistance to the neuromuscular blocking action of

The use of cisatracurium before succinylcholine to

established with certainty.

In addition to adverse events reported from clinical trials,

CISATRACURIUM

and 20 x the human ED95 dose, respectively, revealed no

Teratology testing in nonventilated pregnant rats treated

concentration (30 mcg/mL) and incubation time (4 hours)

(Carcinogenesis, Mutagenesis, Impairment of Fertility

been demonstrated in patients chronically administered

Long-Term Use in the Intensive Care Unit (ICU)

One of two intubating doses of cisatracurium may be

observed in Clinical Trials of Intensive Care Unit

intubation conditions. These patients usually had predisposing causes (such as

of potency. Dilutions to 0.1 mg/mL or 0.2 mg/mL in 5%

5% Dextrose and 0.9% Sodium Chloride Injection, USP

Fresenius Kabi USA, LLC

Lake Zurich, IL 60047

Cisatracurium Besylate Injection is supplied as:

•  ALFENTA®

• 0.9% Sodium Chloride Injection, USP

diluted as directed

NDC

416020 63323-418-20 200 mg/20 mL

MIL


Table 10. Infusion Rates of Cisatracurium for

Table 11. Infusion Rates of Cisatracurium for

Weight (kg) Infusion Delivery Rate (mL/hr)

10 1.5 2.3 3 5

60 90 120 180 300

Table 11. Infusions Rates of Cisatracurium for

Infants

Table 10. Infusion Rates of Cisatracurium for

Table 10. Infusion Rates of Cisatracurium for

Weight (kg) Infusion Delivery Rate (mL/hr)

10 6 9 12 18 30

45 27 41 54 81 130

70 42 63 84 126 210

100 60 90 120 180 300

Drug Delivery Rate (mcg/kg/min)

Patient

1 1.5 2 3 5

Infusion Rate (mL/hr)

Weight (kg)

10 1.5 2.3 3 4.5 7.5

45 6.8 10.1 15.3 20.3 33.8

70 10.2 15.3 21.3 31.5 52.5

100 15 22.3 30 45 75

Drug Delivery Rate (mcg/kg/min)

Patient

Weight (kg)

1 1.5 2 3 5

Infusion Rate (mL/hr)

Weight (kg)

10 0.8 2 3 4 5

45 2.0 3.8 5.7 8.5 12

70 2.5 4.8 7.1 10.5 15

100 3.0 5.3 7.6 11.0 15.5

5AI

Y-site Administration

In addition to adverse events reported from clinical trials, the following events have been identified during post

administration of cisatracurium in conjunction with one or more anesthetic agents in clinical practice. Because they

are reported voluntarily from a population of uncertain 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.

General

Histamine release, hypersensitivity reactions including anaphylactic or anaphylactoid reactions: which in some cases have been life threatening and fatal. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency (see WARNINGS and PRECAUTIONS).

There are rare reports of wheezing, laryngospasm, bronchoconstriction, and airway obstruction following administration of cisatracurium in children. These reported adverse events were observed during laryngoscopy and endotracheal intubation and the etiology could not be established with certainty.

Musculoskeletal

Prolonged neuromuscular block, inadequate neuromuscular block, muscle weakness, and myopathy.

OVERTOXICATION:

Overtreatment with cisatracurium may result in neuro muscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until return of muscular function is achieved.

Once recovery from neuromuscular block begins, further recovery may be facilitated by administration of an anti

Neuromuscular blocking agents may have a profound

administration of a single bolus dose.

Reduction of the infusion rate by up to 30% to 40% should be considered when cisatracurium is administered during nitrous oxide/oxygen anesthesia. Cisatracurium is

Infusion in the Intensive Care Unit (ICU)

The Infusion of cisatracurium in the OR and ICU are also applicable to use in the ICU. An infusion rate of approximately 3 mcg/kg/min (range: 0.5 to 10.2 mcg/kg/ min) should provide adequate neuromuscular block in adult patients in the ICU. There may be wide interpatient variability in dosage requirements and these may increase or decrease with time (see PRECAUTIONS, Long-term Use in the Intensive Care Unit [ICU]). Following recovery from neuromuscular block after administration of a bolus dose may be necessary to quickly re-establish neuromuscular block prior to reintubation of the intubation conditions.

Infusion Rate Tables

The amount of infusion solution required per minute will depend upon the concentration of cisatracurium in the infusion solution, the desired dose of cisatracurium, and the rate of administration. Consideration to the fluid requirements of the patient also must be considered. Tables 10 and 11 provide guidelines for delivery in mL/hr (equivalent to mcg/kg/min) when 60 microliters = 1 mL of cisatracurium solution in concentrations of 0.1 mg/mL (10 mg/100 mL) or 0.4 mg/mL (40 mg/100 mL).
Cisatracurium Besylate Injection Compatibility and Admixtures

Y-site Administration
Cisatracurium Besylate Injection is acidic (pH = 3.25 to 3.65) and may not be compatible with alkaline solution having a pH greater than 8.5 (e.g., barbiturate solutions). Studies have shown that Cisatracurium Besylate Injection is compatible with:

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- SUFENTANA® (sufentanil citrate) injection, diluted as directed
- ALFENATE® (alfentanil hydrochloride) injection, diluted as directed
- SUBLIMAL® (fentanyl citrate) injection, diluted as directed
- VERSED® midazolam hydrochloride) injection, diluted as directed
- Droperidol Injection, diluted as directed

Cisatracurium Besylate Injection is not compatible with DIPRIVAN® (propofol) Injection or TORADOL® (ketorolac) Injection for Y-site administration. Studies of other parenteral products have not been conducted.

Dilution Stability
Cisatracurium Besylate Injection diluted in 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP, or 5% Dextrose and 0.9% Sodium Chloride Injection, USP to 0.1 mg/mL may be stored either under refrigeration or at room temperature for 24 hours without significant loss of potency. Dilutions to 0.1 mg/mL or 0.2 mg/mL in 5% Dextrose and Lactated Ringer’s Injection may be stored under refrigeration for 24 hours.

Cisatracurium Besylate Injection should not be diluted in Lactated Ringer’s Injection, USP due to chemical instability.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are not clear, or contain visible particulates, should not be used. Cisatracurium Besylate Injection is a colorless to slightly yellow or greenish-yellow solution.

HOW SUPPLIED:
Cisatracurium Besylate Injection is supplied as:

<table>
<thead>
<tr>
<th>Product No.</th>
<th>NDC No.</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>416020</td>
<td>63323-416-05</td>
<td>10 mg/5 mL (2 mg/mL)</td>
</tr>
<tr>
<td></td>
<td>63323-416-10</td>
<td>20 mg/10 mL (2 mg/mL)</td>
</tr>
</tbody>
</table>

NOTE: 10 mL Multiple dose vials contain 0.9% w/v benzyl alcohol as a preservative (see WARNINGS concerning newborn infants).

Cisatracurium Besylate Injection is supplied as:

<table>
<thead>
<tr>
<th>Product No.</th>
<th>NDC No.</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>417018</td>
<td>63323-417-05</td>
<td>10 mg/5 mL (2 mg/mL)</td>
</tr>
<tr>
<td></td>
<td>63323-417-10</td>
<td>20 mg/10 mL (2 mg/mL)</td>
</tr>
</tbody>
</table>

Intended only for use in the ICU.

Storage
Cisatracurium Besylate Injection should be refrigerated at 2° to 8°C (36°F to 46°F) in the carton to preserve potency. Protect from light. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Cisatracurium Besylate Injection within 21 days even if rerefrigerated.

The container closure is not made with natural rubber latex.

The brand names mentioned in this document are the trademarks of their respective owners.

FRESENIUS KABI
Fresenius Kabi USA, LLC
Lake Zurich, IL 60047
451248A
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