PRODUCT MONOGRAPH

[Pr]AJ-CISATRACURIUM
Cisatracurium Besylate Injection

Solution for injection

2 mg/mL cisatracurium (as cisatracurium besylate)

10 mL multiple dose vial

Non-depolarizing Skeletal Neuromuscular Blocking Agent

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

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Cisatracurium Besylate Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous	Solution for Injection / 2 mg/mL – 10 mL fill	Benzyl alcohol, benzenesulfonic acid, water for injection.

AJ-CISATRACURIUM 2 mg/mL – 10 mL contains benzyl alcohol, not for use in neonates. See CONTRAINDICATION and WARNINGS AND PRECAUTIONS.

INDICATIONS AND CLINICAL USE

AJ-CISATRACURIUM (Cisatracurium Besylate Injection) is a non-depolarizing skeletal neuromuscular blocking agent with an intermediate onset and duration of action indicated as an adjunct to general anesthesia, to facilitate non-emergency endotracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

Geriatrics (> 65 years of age):

The time to maximum block is about 1 minute slower in the elderly. For details, see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment, Elderly and Renal Failure Patients.**

Pediatrics (≤ 12 years of age):

For children 2 to 12 years of age, dosage adjustment is required; see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Children, Initial Doses.**

CONTRAINDICATIONS

AJ-CISATRACURIUM 2 mg/mL – 10 mL contains benzyl alcohol, which is used as a preservative. It is contraindicated in:

- Neonates (infants less than 1 month of age) and low birth weight infants. See **WARNINGS AND PRECAUTIONS, General** and **WARNINGS AND PRECAUTIONS, Special Population, Pediatrics**.
- Patients who are hypersensitive to AJ-CISATRACURIUM or to ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Patients who are hypersensitive to any other bis-benzylisoquinolinium agents

- Patients with a known hypersensitivity to benzyl alcohol.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

AJ-CISATRACURIUM should be administered in carefully adjusted dosage by or under the supervision of experienced clinicians who are familiar with the drug's actions and the possible complications of its use. The drug should not be administered unless personnel and facilities for resuscitation and life support (tracheal intubation, artificial ventilation, oxygen therapy), and an antagonist of cisatracurium besylate are immediately available. It is recommended that a peripheral nerve stimulator be used to measure neuromuscular function during the administration of cisatracurium besylate in order to monitor drug effect, determine the need for additional doses, and confirm recovery from neuromuscular block.

AJ-CISATRACURIUM has no known effect on consciousness, pain threshold, thinking, or memory. To avoid distress to the patient, neuromuscular block should not be induced before unconsciousness.

General

Because of its intermediate onset of action, AJ-CISATRACURIUM is not recommended for rapid sequence endotracheal intubation.

Patients subjected to hypothermia may necessitate a reduction in the rate of infusion of AJ-CISATRACURIUM (see **DOSAGE AND ADMINISTRATION**).

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of pre-eclampsia or eclampsia.

As AJ-CISATRACURIUM has not been studied in patients with asthma, it should be administered with caution to these patient groups. See **WARNINGS AND PRECAUTIONS**, **Sensitivity/ Resistance**, **Anaphylaxis** and **Allergic Reactions.**

No data are available to support the use of AJ-CISATRACURIUM by intramuscular injection.

AJ-CISATRACURIUM is acidic (pH 3.25 to 3.65) and should not be mixed with alkaline solutions having a pH greater than 8.5 (e.g., barbiturate solutions). AJ-CISATRACURIUM is also hypotonic and must not be administered into the infusion line of a blood transfusion.

The multiple-dose vials of AJ-CISATRACURIUM contain benzyl alcohol, which is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been 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 flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administration. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources. Single-use vials (5 mL) of AJ-CISATRACURIUM do not contain benzyl alcohol. See **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pediatrics**.

Carcinogenesis and Mutagenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of cisatracurium besylate.

Cisatracurium besylate was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, a rat bone marrow cytogenic assay, and in in vitro human lymphocyte cytogenetics assay. As was the case with atracurium, the mouse lymphoma assay was positive both in the presence and absence of exogenous metabolic activation (rat live S-9). In the absence of S-9, cisatracurium besylate was positive at in vitro cisatracurium concentrations of 40 mcg/mL and higher. In the presence of S-9, cisatracurium besylate was positive at a cisatracurium concentration of 300 mcg/mL but not at lower or higher concentrations.

Cardiovascular

Recommended doses of AJ-CISATRACURIUM have no clinically significant effects on heart rate; therefore, AJ-CISATRACURIUM will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Endocrine and Metabolism

Malignant Hyperthermia (MH)

In a study of MH-susceptible pigs, cisatracurium besylate did not trigger MH. AJ-CISATRACURIUM has not been studied in MH-susceptible patients. Because MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia.

Hepatic/Biliary/Pancreatic

Hepatic

See **WARNINGS AND PRECAUTIONS**, **Renal and Hepatic** for details.

Neurologic

Patients with hemiparesis or paraparesis also may demonstrate resistance to non-depolarizing neuromuscular blocking agents in affected limbs. To avoid inaccurate dosing, neuromuscular monitoring should be performed on the non-paretic limb.

In patients with neuromuscular disease such as myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. In these patients, and patients with conditions in which prolonged neuromuscular blockade is a possibility (e.g. neuromuscular disease, carcinomatosis, severe cachexia or debilitation), the use of a peripheral nerve stimulator and a first dose of not more than 0.02 mg/kg AJ-CISATRACURIUM is recommended to assess the level of neuromuscular block and to monitor dosage requirements.

Intensive Care Unit (ICU)

Whenever the use of AJ-CISATRACURIUM, or any neuromuscular blocking agent, is contemplated in the ICU, it is recommended that a peripheral nerve stimulator be used to continuously monitor neuromuscular transmission during administration and recovery. Additional doses of AJ-CISATRACURIUM or any other neuromuscular blocking agent should not be given before there is evidence of the return of the first twitch response to peripheral nerve stimulation. If no response is elicited, the infusion should be discontinued until a response returns.

Long-Term Use in the ICU:

To reduce the possibility of prolonged neuromuscular blockade and other complications that might occur following long-term use in the ICU, AJ-CISATRACURIUM, or any other neuromuscular relaxant, should be administered in carefully adjusted doses by or under the supervision of experienced clinicians who are familiar with its actions and with appropriate peripheral nerve stimulator muscle monitoring techniques.

Continuous infusion or intermittent bolus dosing to support long-term mechanical ventilation has not been studied sufficiently to support dosage recommendations. There is limited information regarding the safety and efficacy of long-term infusion of cisatracurium besylate during mechanical ventilation in the ICU (up to 2 days n=37, 2 to 4 days n=19, 4 to 6 days n=12) and no information on its use beyond 6 days. Thus dosage recommendations cannot be made at this time. In rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation in ICU settings has been associated with prolonged paralysis and/or skeletal muscle weakness that is first noted during attempts to wean patients from the ventilator. In these patients, the actions of the neuromuscular blocking agent may be enhanced by other drugs (e.g., broad spectrum antibiotics, narcotics and/or steroids) or by conditions such as acid-base or electrolyte imbalance, hypoxic episodes of varying duration, or extreme debilitation. Additionally patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy Recovery may vary from regaining movement and strength in all muscles to initial recovery of movement of the facial muscles and small muscles of the extremities then to the remaining muscles. In rare cases, recovery may involve an extended period of time or even require rehabilitation. Therefore, when there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. The syndrome of critical illness polyneurophathy associated with sepsis and multiorgan failure may be associated with prolonged muscle paralysis, but can also occur without the use of muscle relaxants. Thus, the role of muscle relaxants in the etiology of prolonged paralysis in the ICU is not known with certainty.

Renal and Hepatic

Cisatracurium undergoes degradation in the body at physiological pH and temperature by organ-independent Hofmann elimination to form laudanosine and the monoquaternary acrylate metabolite. No clinically significant alterations in the recovery profile were observed in patients with renal impairment or hepatic impairment following a 0.1 mg/kg (2 x ED_{95}; twice the dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) dose of cisatracurium. The onset time was approximately 1 minute faster in patients with end-stage liver disease and approximately 1 minute slower in patients with renal dysfunction than in healthy adult control patients.

Sensitivity/Resistance

Anaphylaxis

Severe anaphylactic reactions to neuromuscular blocking agents, including AJ-CISATRACURIUM, have been reported. These reactions have in some cases been life threatening and fatal. Due to the potential severity of these reactions, the necessary precautions, such as immediate availability of appropriate emergency treatment, should be taken. Precautions should also be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents since cross-reactivity between neuromuscular blocking agents, both depolarizing and non- depolarizing, has been reported in this class of drugs.

Allergic Reactions

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

Burns

Patients with burns have been shown to develop resistance to non-depolarizing 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. AJ-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 AJ-CISATRACURIUM is administered to burn patients.

Special Populations

Pregnant Women

Teratology testing in rats revealed no maternal or fetal toxicity or teratogenic effects. See **TOXICOLOGY, Reproduction and Teratology**. There are no adequate and well-controlled studies of AJ-CISATRACURIUM in pregnant women. Because animal studies are not always predictive of human response, AJ-CISATRACURIUM should be used during pregnancy only if clearly needed.

Labour and Delivery

The use of AJ-CISATRACURIUM during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether cisatracurium besylate administered to the mother has effects on the fetus. Doses of 0.2 or 0.4 mg/kg (4 x or 8 x human ED_{95}) cisatracurium besylate given to female beagles undergoing cesarean section resulted in negligible levels of cisatracurium besylate in umbilical vessel blood of neonates and no deleterious effects on the pups.

Nursing Women

It is not known whether cisatracurium besylate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following administration of AJ-CISATRACURIUM to a nursing woman.

Pediatrics (≤ 12 *years of age*)

For children 2 – 12 years of age, a lower dose should be used. AJ-CISATRACURIUM has not been studied in children under 2 years of age (see **ACTION AND CLINICAL PHARMACOLOGY** for clinical experience and **DOSAGE AND ADMINISTRATION** for recommendations for use in children 2 to 12 years of age).

The 10 mL multiple-dose vials of AJ-CISATRACURIUM contain benzyl alcohol as a preservative. Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome", (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in blood and urine) has been associated with benzyl alcohol dosages > 99 mg/kg/day in neonates (infants less than 1 month of age) and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. AJ-CISATRACURIUM should not be used in neonates. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity.

Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources. See CONTRAINDICATIONS.

Geriatrics (≥ 65 years of age)

Cisatracurium besylate was safely administered during clinical trials to 130 elderly (≥65 years) patients, including a subset of patients with significant cardiovascular disease. See **WARNINGS AND PRECAUTIONS, General**.

Minor differences in the pharmacokinetics of cisatracurium between elderly and young adult patients are not associated with clinically significant differences in the recovery profile of cisatracurium following a single 0.1 mg/kg (2 x ED_{95}) dose; however, the time to maximum block is approximately one minute slower in elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

The effects of hemofiltration, hemodialysis, and hemoperfusion on plasma levels of cisatracurium besylate and its metabolites are unknown.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse experiences were uncommon among the 908 surgical patients who received cisatracurium in conjunction with other drugs in U.S. and European clinical studies in the course of a wide variety of procedures in patients receiving opioid, propofol, or inhalation anesthesia.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse experiences were judged by investigators during the clinical trials to have a possible causal relationship to cisatracurium (incidence less than 1%):

Cardiovascular System: Flushing (0.2%), hypotension (0.2%), bradycardia (0.4%)

Respiratory System: Bronchospasm (0.2%)

Skin and Appendages: Rash (0.1%)

Post-Market Adverse Drug Reactions

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

General: 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, bronchospasm, rash and itching following administration of cisatracurium in children. These reported adverse events were not serious and their etiology could not be established with certainty.

Musculoskeletal System: Prolonged neuromuscular block, and inadequate neuromuscular block.

DRUG INTERACTIONS

Drug-Drug Interactions

Succinylcholine

The use of AJ-CISATRACURIUM prior to succinylcholine, for the purpose of attenuating succinylcholine-induced side effects, has not been studied.

The use of cisatracurium besylate following varying degrees of recovery from succinylcholine-induced neuromuscular block has been assessed in a limited number of patients. Administration of 0.1 mg/kg (2 x ED_{95}) cisatracurium at 10% (n=15) or 95% recovery (n=15) following an intubating dose of succinylcholine (1 mg/kg) produced ≥ 95% neuromuscular block. The time of onset of maximum block following AJ-CISATRACURIUM is approximately 2 minutes faster with prior administration of succinylcholine. Prior administration of succinylcholine had no effect on the duration of neuromuscular block following initial or maintenance bolus doses of AJ-CISATRACURIUM. Cisatracurium besylate infusion requirements were comparable or slightly greater in patients who received succinylcholine prior to the cisatracurium besylate infusions, in contrast to patients who did not receive succinylcholine.

Other non-depolarizing Muscle Relaxants

Although not studied systematically in clinical trials, no drug interactions were observed when vecuronium, pancuronium, or atracurium were administered following varying degrees of recovery from single doses or infusions of cisatracurium.

Inhalation Anesthetics

Inhalational anesthetics may prolong the clinically effective duration of action of initial and maintenance doses of AJ-CISATRACURIUM, and decrease the average infusion rate of AJ-CISATRACURIUM. The magnitude of these effects may depend on the duration of administration of the volatile agents (see **DOSAGE AND ADMINISTRATION**, Maintenance Doses and **ACTION AND CLINICAL PHARMACOLOGY)**.

Intravenous Anesthetics

In clinical studies, propofol had no effect on the duration of action or dosing requirements for cisatracurium.

Anticonvulsants

Resistance to the neuromuscular blocking action of non-depolarizing neuromuscular blocking agents has been demonstrated in patients chronically administered phenytoin or carbamazepine. While the effects of chronic phenytoin or carbamazepine therapy on the action of cisatracurium besylate are unknown, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher.

Other drugs

The neuromuscular blocking action of non-depolarizing agents such as cisatracurium besylate may be enhanced by certain antibiotics (e.g., aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistemethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

There are no known drug-laboratory interactions.

Drug-Lifestyle Interactions

There are no known drug-lifestyle interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The 10 mL multiple dose vials of AJ-CISATRACURIUM contain benzyl alcohol. See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**.

- AJ-CISATRACURIUM should be administered only by the intravenous route. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case.

- To avoid patient distress, AJ-CISATRACURIUM should NOT be administered prior to the induction of unconsciousness. It should NOT be mixed in the same syringe or administered simultaneously through the same needle with alkaline solutions (e.g. barbiturate solutions).

Recommended Dose and Dosage Adjustment

The dosage information provided below is intended as a guide only. Doses AJ-CISATRACURIUM should be individualized and a peripheral nerve stimulator should be used to measure neuromuscular function during administration of AJ-CISATRACURIUM in order to monitor drug effect, to determine the need for additional doses, and to confirm recovery from neuromuscular block. The use of a peripheral nerve stimulator will permit the

most advantageous use of AJ-CISATRACURIUM; minimize the possibility of over dosage or under dosage, and assist in the evaluation of recovery.

Adults:

Initial Doses

One of two intubating doses of cisatracurium may be chosen, based on the desired time to intubation and the anticipated length of surgery. Doses of 0.15 mg/kg (3 x ED_{95}) and 0.20 mg/kg (4 x ED_{95}) cisatracurium, as components of a propofol/nitrous oxide/oxygen induction-intubation technique, may each produce generally good or excellent conditions for intratracheal intubation in 1.5 to 2.0 minutes. The clinically effective durations of action for 0.15 and 0.20 mg/kg cisatracurium during propofol anesthesia are 55 minutes (range: 44 to 74 min) and 61 minutes (range: 41 to 81 min), respectively. Lower doses may result in a longer time for the development of satisfactory intubation conditions. In addition to the dose of the neuromuscular blocking agent, the presence of co-induction agents (e.g., fentanyl and midazolam) and the depth of anesthesia are factors that can influence intubation conditions. Doses of cisatracurium up to 8 times the ED_{95} (0.40 mg/kg) have been administered to a limited number of healthy adult patients (n=15) and patients with serious cardiovascular disease (n=31). These larger doses are associated with a longer clinically effective duration of action (see **ACTION AND CLINICAL PHARMACOLOGY**).

Cardiovascular Disease

AJ-CISATRACURIUM doses of up to 0.30 mg/kg (6 x ED_{95}) cisatracurium were found to have no significant hemodynamic effects in patients with cardiovascular disease (New York Heart Association Class I-III). There are limited data for doses above 0.30 mg/kg in this patient population. At a dose of 0.10 mg/kg an extension of the interval between administration of AJ-CISATRACURIUM and the intubation attempt may be required to achieve satisfactory intubation conditions.

Elderly and Renal Failure Patients

Because a slower time to onset of complete neuromuscular block was observed in elderly patients and in patients with renal failure, extending the interval between administration of AJ-CISATRACURIUM and the intubation attempt for these patients may be required to achieve adequate intubation conditions.

Maintenance dosing

A dose of 0.03 mg/kg cisatracurium is recommended for maintenance of neuromuscular block during prolonged surgical procedures. Maintenance doses of 0.03 mg/kg each sustain neuromuscular block for approximately 20 minutes. Although maintenance dosing is generally required 40 to 50 minutes following an initial dose of 0.15 mg/kg (3 x ED_{95}) AJ-CISATRACURIUM and 50 to 60 minutes following an initial dose of 0.20 mg/kg (4 x ED_{95}) AJ-CISATRACURIUM, the need for maintenance doses should be determined by clinical criteria. For a shorter or longer duration of action, smaller or larger maintenance doses may be administered.

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. 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 AJ-CISATRACURIUM; therefore, no adjustment to the initial dose should be necessary when AJ-CISATRACURIUM is administered shortly after initiation of volatile agents. In long surgical procedures during enflurane or isoflurane anesthesia, less frequent maintenance dosing or lower maintenance doses of AJ-CISATRACURIUM may be necessary.

No adjustments to the initial dose of AJ-CISATRACURIUM are required when used in patients receiving propofol anesthesia.

Children:

Initial Doses

The recommended dose of AJ-CISATRACURIUM for children 2 to 12 years of age is 0.10 mg/kg of cisatracurium administered over 5 to 10 seconds during either halothane or opioid anesthesia. When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.10 mg/kg cisatracurium produces maximum neuromuscular block in an average of 2.8 minutes (range: 1.8 to 6.7 min) and clinically effective block for an average of 28 minutes (range: 21 to 38 min). AJ-CISATRACURIUM has not been studied in children under 2 years of age.

Special Conditions:

Based on the known action of cisatracurium besylate and other neuromuscular blocking agents, the following factors should be considered when administering AJ-CISATRACURIUM:

Renal and Hepatic Disease

Doses for patients with renal or hepatic impairment are as recommended for healthy adult patients. However, the onset time may be slightly faster in patients with liver impairment and slightly slower in patients with renal impairment. See **WARNINGS AND PRECAUTIONS, Renal and Hepatic.**

Drugs or Conditions Causing Potentiation of, or Resistance to, Neuromuscular Block

Patients with hemiparesis or paraparesis may be more resistant to cisatracurium, whereas those with myasthenia, myasthenic syndrome, or some other neuromuscular diseases may be more susceptible to the effect of cisatracurium. See **WARNINGS AND PRECAUTIONS, Neurologic.**

Patients with burns have been shown to develop resistance to non-depolarizing neuromuscular blocking agents, and may require adjustment to dosing (see **WARNINGS AND PRECAUTIONS, Burns**).

Concomitant use of cisatracurium with anticonvulsants, certain antibiotics, magnesium salts, lithium, local anesthetics, procainamide, and quinidine may affect the action of duration of cisatracurium. See **DRUG INTERACTIONS, Drug-Drug Interactions**.

Hypothermia

The rate of infusion of atracurium required to maintain adequate surgical relaxation in patients undergoing coronary artery bypass surgery with induced hypothermia (25° to 28°C) is approximately half the rate required during normothermia. Based on the structural similarity between cisatracurium besylate and atracurium, a similar effect on the infusion rate of AJ-CISATRACURIUM may be expected.

Use by Continuous Infusion:

Infusion in the Operating Room (OR)

After administration of an initial bolus dose of AJ-CISATRACURIUM, a diluted solution of AJ-CISATRACURIUM can be administered by continuous infusion to adults and children (≥2 years of age) for maintenance of neuromuscular block during extended surgical procedures. Infusion of cisatracurium besylate should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation. Accurate dosing is best achieved using a precision infusion device.

Infusion of cisatracurium besylate should be initiated only after early evidence of spontaneous recovery from the initial bolus dose. An initial infusion rate of 3 mcg/kg/min cisatracurium besylate may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 1 to 2 mcg/kg/min should be adequate to maintain continuous neuromuscular block in the range of 89% to 99% in most pediatric and adult patients under opioid/nitrous oxide/oxygen anesthesia.

Reduction of the infusion rate by up to 30% to 40% should be considered when cisatracurium besylate is administered during stable isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC). Greater reductions in the infusion rate of cisatracurium besylate may be required with longer durations of administration of isoflurane or enflurane.

Spontaneous recovery from neuromuscular block following discontinuation of cisatracurium besylate infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

Infusion Rate Tables:

The amount of infusion solution required per minute will depend upon the concentration of cisatracurium besylate in the infusion solution, the desired dose of cisatracurium besylate, and the patient's weight. The contribution of the infusion solution to the fluid requirements of the patient also must be considered. Tables 1 and 2 provide guidelines for delivery in mL/hr (equivalent to microdrops/min when 60 microdrops = 1 mL) of cisatracurium besylate solutions in concentrations of 0.1 mg/mL (10 mg/100 mL) or 0.4 mg/mL (40 mg/100 mL) of cisatracurium.

Table 1 **Cisatracurium Besylate Infusion Rates for Maintenance of Neuromuscular Block during Opioid/Nitrous Oxide/Oxygen Anesthesia Using Cisatracurium at a Concentration of 0.1 mg/mL**

Patient Weight (kg)	Cisatracurium Besylate Delivery Rate (mcg/kg/min)				
	1	1.5	2	3	5
	Infusion Delivery Rate (mL/hr)				
10	6	9	12	18	30
45	27	41	54	81	135
70	42	63	84	126	210
100	60	90	120	180	300

Table 2 **Cisatracurium Besylate Infusion Rates for Maintenance of Neuromuscular Block during Opioid/Nitrous Oxide/Oxygen Anesthesia Using Cisatracurium at a Concentration of 0.4 mg/mL**

Patient Weight (kg)	Cisatracurium Besylate Delivery Rate (mcg/kg/min)				
	1	1.5	2	3	5
	Infusion Delivery Rate (mL/hr)				
10	1.5	2.3	3	4.5	7.5
45	6.8	10.1	13.5	20.3	33.8
70	10.5	15.8	21	31.5	52.5
100	15	22.5	30	45	75

Administration

Special Considerations for Administration

Y-site Administration:

AJ-CISATRACURIUM 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 AJ-CISATRACURIUM is compatible with:

- 5% Dextrose Injection USP
- 0.9% Sodium Chloride Injection USP
- 5% Dextrose and 0.9% Sodium Chloride Injection USP
- Sufentanil Citrate Injection, diluted as directed
- Alfentanil hydrochloride injection, diluted as directed
- Fentanyl citrate injection, diluted as directed
- Midazolam hydrochloride injection, diluted as directed
- Droperidol Injection USP, diluted as directed

AJ-CISATRACURIUM is not compatible with propofol injection or ketorolac tromethamine injection for Y-site administration. Studies of other parenteral products have not been conducted.

Antagonism of Neuromuscular Block

Antagonists (such as neostigmine and edrophonium) should not be administered when complete neuromuscular block is evident or suspected. The use of a peripheral nerve stimulator to evaluate recovery and antagonism of neuromuscular block is recommended. The time required for anticholinesterase mediated recovery is longer for reversals attempted at deeper levels of blockade.

Administration of 0.04 to 0.07 mg/kg neostigmine at approximately 10% recovery from neuromuscular block (range: 0% to 15%) produced 95% recovery of the muscle twitch response and a T4:T1 ratio ≥ 70% in an average of 9 to 10 minutes. The time from 25% recovery of the muscle twitch response to a T4:T1 ratio ≥ 70% following these doses of neostigmine averaged 7 minutes. The mean 25 to 75% recovery index following reversal was 3 to 4 minutes.

Administration of 1.0 mg/kg edrophonium at approximately 25% recovery from neuromuscular block (range: 16% to 30%) produced 95% recovery and a T4:T1 ratio ≥ 70% in an average of 3 to 5 minutes.

Patients administered antagonists should be evaluated for evidence of adequate clinical recovery (e.g., 5-second head lift and grip strength). Ventilation must be supported until no longer required.

The onset of antagonism may be delayed in the presence of debilitation, cachexia, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **DRUG INTERACTIONS**). Under such circumstances the management is the same as that of prolonged neuromuscular block (see **OVERDOSAGE**).

OVERDOSAGE

Over dosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once recovery from neuromuscular block begins, further recovery may be facilitated by administration of an anticholinesterase agent (e.g., neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent. See **DOSAGE AND ADMINISTRATION**, **Antagonism of Neuromuscular Block**. A peripheral nerve stimulator should be used to monitor recovery.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AJ-CISATRACURIUM is an intermediate-acting, non-depolarizing neuromuscular blocking agent for intravenous administration. Cisatracurium besylate, one of 10 isomers of atracurium besylate, constitutes approximately 15% of atracurium besylate. Cisatracurium besylate binds competitively to cholinergic receptors on the motor endplate to antagonize the action of acetylcholine, resulting in block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors such as neostigmine and edrophonium.

Pharmacodynamics

The average ED_{95} (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 mg/kg) in adults receiving opioid/nitrous oxide/oxygen anesthesia. For comparison, the average ED_{95} for atracurium when also expressed as the parent biscation is 0.17 mg/kg under similar anesthetic conditions. When the dose of cisatracurium is doubled, the clinically effective duration of block increased by approximately 25 to 35 minutes. Once recovery begins, the rate of recovery is independent of dose.

The pharmacodynamics of 2 to 8 times the ED_{95} (0.1 to 0.4 mg/kg) of cisatracurium administered over 5 to 10 seconds during opioid/nitrous oxide/oxygen anesthesia are summarized in **Table 3.**

The neuromuscular blocking potency of cisatracurium besylate is approximately three-fold that of atracurium besylate. At equipotent doses, the time to maximum block of cisatracurium besylate is up to 2 minutes longer than that of atracurium besylate. The clinically effective duration of action and rate of spontaneous recovery from equipotent doses of cisatracurium besylate and atracurium besylate are similar.

The neuromuscular blocking effect of cisatracurium besylate administered by infusion is potentiated by potent inhalation anesthetics. Isoflurane or enflurane administered with nitrous oxide/oxygen to achieve 1.25 MAC may prolong the clinically effective duration of action of initial and maintenance doses, and decrease the average infusion rate requirement of cisatracurium besylate. 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 besylate and therefore, no adjustment to the initial dose should be necessary when cisatracurium besylate 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 besylate may be necessary. As for atracurium, the average infusion rate requirement for cisatracurium besylate may be decreased under these circumstances by as much as 30% to 40%.

The onset, duration of action, and recovery profiles of cisatracurium besylate during propofol/oxygen or propofol/nitrous oxide/oxygen anesthesia are similar to those during opioid/nitrous oxide/oxygen anesthesia.

Table 3 Pharmacodynamic Dose Response* of Cisatracurium Besylate Administered Over 5 to 10 Seconds during Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial Dose of cisatracurium besylate (mg/kg)	Time to 90% Block (min)	Time to Maximum Block (min)	Time to Spontaneous Recovery*				25% to 75% Recovery Index (min)
			5% Recovery (min)	25% Recovery [a] (min)	95% Recovery (min)	$T_4:T_1$ Ratio [b] ≥70% (min)	
Adults							
0.1 ($2xED_{95}$) n = 98	3.3 (1.0-8.7)	5.0 (1.2-17.2)	33 (15-51)	42 (22-63)	64 (25-93)	64 (32-91)	13 (5-30)
0.15[c] ($3xED_{95}$) n=39	2.6 (1.0-4.4)	3.5 (1.6-6.8)	46 (28-65)	55 (44-74)	76 (60-103)	75 (63-98)	13 (11-16)
0.2 ($4xED_{95}$) n=30	2.4 (1.5-4.5)	2.9 (1.9-5.2)	59 (31-103)	65 (43-103)	81 (53-114)	85 (55-114)	12 (2-30)
0.25 ($5xED_{95}$) n=15	1.6 (0.8-3.3)	2.0 (1.2-3.7)	70 (58-85)	78 (66-86)	91 (76-109)	97 (82-113)	8 (5-12)
0.4 ($8xED_{95}$) n=15	1.5 (1.3-1.8)	1.9 (1.4-2.3)	83 (37-103)	91 (59-107)	121 (110-134)	126 (115-137)	14 (10-18)
Children (2 to 12 years of age)							
0.08[d] ($2xED_{95}$) n=60	2.2 (1.2-6.8)	3.3 (1.7-9.7)	22 (11-38)	29 (20-46)	52 (37-64)	50 (37-62)	11 (7-15)
0.1 n=16	1.7 (1.3-2.7)	2.8 (1.8-6.7)	21 (13-31)	28 (21-38)	46 (37-58)	44 (36-58)	10 (7-12)

* Values shown are medians of means from individual studies. Values in parentheses are ranges of individual patient values.
[a] Clinically effective duration of block
[b] Train-of-four ratio
[c] Propofol anesthesia
[d] Halothane anesthesia
*Not all patients (~50%) were evaluated for spontaneous recovery parameters
Definitions: min = minute; n = the number of patients with Time to Maximum Block data

Intubation Conditions

When administered during the induction of adequate anesthesia using propofol, nitrous oxide/oxygen, and co-induction agents (e.g., fentanyl, midazolam), good or excellent conditions for tracheal intubation occurred in 67/71 (94%) patients in 1.5 to 2.0 minutes following 0.15 mg/kg (3 x ED_{95}) cisatracurium and in 69/80 (87%) patients in 1.5 minutes following 0.2 mg/kg (4 x ED_{95}) cisatracurium. Favorable intubation conditions, within 2.0 minutes, were achieved less frequently with a cisatracurium dose of 0.1 mg/kg (2 x ED_{95}).

Maintenance Doses

Repeated administration of maintenance doses or a continuous infusion of cisatracurium besylate 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 therefore 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 infusion and comparable to the rate of recovery following initial doses **(**see **Table 3).**

Anticholinesterase Antagonism

The neuromuscular block produced by cisatracurium besylate 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.

Pediatrics

In children (2 to 12 years of age) cisatracurium has a lower ED_{95} than in adults (0.04 mg/kg, halothane/nitrous oxide/oxygen anesthesia). At 0.1 mg/kg during opioid anesthesia, cisatracurium had a faster onset and shorter duration of action in children than in adults **(**see **Table 3)**. Recovery following reversal is faster in children than in adults.

Hemodynamics Profile

No dose-related effects were observed on mean arterial blood pressure (MAP) or heart rate (HR) following doses of cisatracurium ranging from 2 to 8 times the ED_{95} (0.1 mg/kg to 0.4 mg/kg), administered over 5 to 10 seconds, in healthy adult patients, or in patients with serious cardiovascular disease.

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 ED_{95} (0.10 mg/kg to 0.40 mg/kg). While the hemodynamic profile was comparable in cisatracurium besylate and active control groups, data for doses above 0.3 mg/kg in this population are limited.

Cisatracurium, at therapeutic doses of 2 to 8 times the ED_{95} (0.10 to 0.40 mg/kg), administered over 5 to 10 seconds, does not cause dose-related elevations in mean plasma histamine concentration.

No clinically significant changes in MAP or HR were observed following administration of doses up to 0.10 mg/kg cisatracurium over 5 to 10 seconds in children (2 to 12 years of age) receiving either halothane/nitrous oxide/oxygen or opioid/nitrous oxide/oxygen anesthesia.

Pharmacokinetics

Following intravenous administration of cisatracurium besylate, plasma concentrations of cisatracurium are best described by a two-compartment open model. Cisatracurium undergoes degradation in the body at physiological pH and temperature by organ-independent Hofmann elimination to form laudanosine and the monoquaternary acrylate metabolite. Laudanosine is further metabolized to many components which are eliminated in the urine. The monoquaternary acrylate metabolite undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite. Cisatracurium does not appear to undergo direct hydrolysis by non-specific plasma esterases. Organ-independent Hofmann elimination appears to be the predominant pathway for the elimination of cisatracurium.

Plasma cisatracurium concentrations and neuromuscular block data from 261 patients in six studies were combined to develop population estimates of the pharmacokinetic/ pharmacodynamic parameters for cisatracurium in healthy adult patients. The plasma clearance was 4.6 mL/min/kg and the volume of distribution at steady state was 145 mL/kg in healthy adult patients receiving opioid/nitrous oxide/oxygen anesthesia. Results from population pharmacokinetic/pharmacodynamic analyses and from conventional pharmacokinetic analyses of cisatracurium in healthy adult patients and in patient subpopulations (e.g., geriatric, pediatric, obese) are described in Special Populations and Conditions.

Dose Proportionality

Conventional pharmacokinetic analysis from a study of 10 healthy adult patients receiving 0.10 mg/kg (2 x ED_{95}) cisatracurium besylate and 10 healthy adult patients receiving 0.20 mg/kg (4 x ED_{95}) cisatracurium besylate showed no statistically significant differences in the pharmacokinetic parameters between the two groups (See **Table 4**). In addition, population pharmacokinetic/pharmacodynamic analyses revealed no statistically significant effect of dose on plasma clearance between 0.10 mg/kg and 0.40 mg/kg (2 to 8 x ED_{95}) doses of cisatracurium. The pharmacokinetics are linear between these doses of cisatracurium (i.e., plasma concentrations are approximately proportional to dose).

Table 4 Pharmacokinetic Parameters* of Cisatracurium in Healthy Adult Patients (Opioid/Nitrous Oxide/Oxygen Anesthesia)

Parameter	Initial Dose of Cisatracurium Besylate (mg/kg)	
	0.1 (2xED_{95}) (n=10)	**0.2 (4xED_{95}) (n=10)**
Elimination t½ β (min)	22.4 ± 2.7	25.5 ± 4.1
Volume of Distribution at Steady State (mL/kg)	144 ± 34	121 ± 22
Plasma Clearance (mL/min/kg)	5.3 ± 1.2	4.7 ± 0.7

*Values presented are mean ± Standard Deviation (SD)
Definitions: SD = Standard Deviation; $t_{1/2}\beta$ = beta half life

Absorption

Not applicable.

Distribution

The volume of distribution at steady state was 145 mL/kg in healthy adult patients receiving opioid/nitrous oxide/oxygen anesthesia.

Metabolism

Tests in which the monoquaternary alcohol metabolite or the monoquaternary acrylate was administered to cats suggest that metabolites are unlikely to produce clinically significant neuromuscular, autonomic, or cardiovascular effects following administration of cisatracurium besylate. Laudanosine, a biologically active metabolite of cisatracurium besylate without neuromuscular blocking activity, produces transient hypotension and, in higher concentrations, cerebral excitatory effects when administered in several species of

animals. The relationship between Central Nervous System (CNS) excitation and laudanosine concentrations in humans has not been established. Because cisatracurium is three times more potent than atracurium and lower doses are required, maximum concentrations of laudanosine following infusions of cisatracurium besylate to surgical patients were lower (5- to 8-fold) than following atracurium besylate. After adjusting for differences in doses, the area under the curve for laudanosine was significantly lower following cisatracurium besylate administration than following atracurium besylate administration (i.e., less laudanosine may be formed following cisatracurium besylate than following atracurium besylate). The clinical relevance of this finding is unknown.

Excretion

The liver and the kidney play a minor role in the elimination of cisatracurium but are primary routes for elimination of the metabolites.

Special Populations and Conditions

Pediatrics

Population pharmacokinetic analysis of cisatracurium revealed a plasma clearance of 5.9 mL/kg/min and a volume of distribution at steady-state of 125 mL/kg in 20 healthy pediatric patients during halothane anesthesia. These minor differences were associated with a faster time to onset and a shorter duration of cisatracurium induced neuromuscular block in pediatric patients.

Geriatrics

The results of conventional pharmacokinetic analysis from a study of 12 healthy elderly patients (≥65 years) and 12 healthy young adult patients (18 to 50 years of age) receiving a single i.v. of 0.10 mg/kg (2 x ED_{95}) cisatracurium besylate are summarized in **Table 5**. Plasma clearance of cisatracurium was not affected by age; however, the volume of distribution was slightly larger in elderly patients than in young patients, resulting in a slightly longer $t_{½}$ (half-life) for cisatracurium. The time to maximum block was approximately one minute slower in elderly patients than in young patients. These minor differences in pharmacokinetics of cisatracurium besylate between elderly and young adult patients were not associated with clinically significant differences in the recovery profile of cisatracurium.

Table 5 **Pharmacokinetic Parameters* of Cisatracurium in Healthy Elderly and Young Adult Patients Following 0.1 mg/kg (2 x ED_{95}) Cisatracurium Besylate (Isoflurane/Nitrous Oxide/Oxygen Anesthesia)**

Parameter	Elderly Patients (n=12)	Young Adult Patients n=12
Elimination $t_{½}$ β (min)	25.8 ± 3.6[a]	22.1 ± 2.5
Volume of Distribution at Steady State (mL/kg)	156 ± 17[a]	133 ± 15
Plasma Clearance (mL/min/kg)	5.7 ± 1.0	5.3 ± 0.9

*Values presented are mean ± SD
[a] $p<0.05$ for comparisons between the two groups
Definitions: SD = Standard Deviation; $t_{½}$ β = beta half life

Gender and Obesity

Population pharmacokinetic/pharmacodynamic analysis revealed that gender and obesity were associated with statistically significant effects on the pharmacokinetics and/or pharmacodynamics of cisatracurium; these factors were not associated with clinically significant alterations in the predicted onset or recovery profile of cisatracurium.

Hepatic Insufficiency

Organ-independent Hofmann elimination is the predominant pathway for the elimination of cisatracurium. **Table 6** summarizes the conventional pharmacokinetic analysis from a study of 13 patients with end-stage liver disease undergoing liver transplantation and 11 healthy adult patients undergoing elective surgery. The slightly larger volume of distribution in liver transplant patients was associated with slightly higher plasma clearance of cisatracurium. The parallel changes in these parameters resulted in no difference in $t_{½}$. The time to maximum block was approximately one minute faster in liver transplant patients than in healthy adult patients. These minor differences in pharmacokinetics were not associated with clinically significant changes in the recovery profile of cisatracurium.

The $t_{1/2}\beta$ (beta half life) values of metabolites are longer in patients with hepatic disease and concentrations may be higher after long-term administration.

Table 6 Pharmacokinetic Parameters* of Cisatracurium in Healthy Adult Patients and in Patients Undergoing Liver Transplantation Following 0.1 mg/kg ($2xED_{95}$) Cisatracurium Besylate (Isoflurane/Nitrous Oxide/Oxygen Anesthesia)

Parameter	Healthy Adult Patients	Liver Transplant Patients
Elimination$t_{½}\beta$ (min)	23.5 ± 3.5	24.4 ± 2.9
Volume of Distribution at Steady State (mL/kg)	161 ± 23	195 ± 38[a]
Plasma Clearance (mL/min/kg)	5.7 ± 0.8	6.6 ± 1.1[a]

*Values presented are mean ±S.D.
[a] $p<0.05$ for comparisons between liver transplant patients and healthy adult patients
Definitions: SD = Standard Deviation; $t_{½}\beta$ = beta half life

Renal Insufficiency

Results from a conventional pharmacokinetic study of 13 healthy adult patients and 15 patients with end-stage renal disease (ESRD) undergoing elective surgery are summarized in **Table 7**. The pharmacokinetics of cisatracurium was similar in healthy adult patients and ESRD patients.

Table 7 Pharmacokinetic Parameters* for Cisatracurium in Healthy Adult Patients and in Patients with End-Stage Renal Disease (ESRD) Receiving 0.1 mg/kg ($2xED_{95}$) Cisatracurium Besylate (Opioid/Nitrous Oxide/Oxygen Anesthesia)

Parameter	Healthy Adult Patients	ESRD Patients
Elimination $t_{½}\beta$ (min)	29.4 ± 4.1	32.3 ± 6.3
Volume of distribution at steady state (mL/kg)	149 ± 35	160 ± 32
Plasma clearance (mL/min/kg)	4.66 ± 0.86	4.26 ± 0.62

*Values presented are mean ± SD
Definitions: SD = Standard Deviation; $t_{½}\beta$ = beta half life

The time to 90% block was approximately one minute slower in ESRD patients following 0.10 mg/kg cisatracurium. There was no difference in the duration or rate of recovery between ESRD and healthy adult patients.

The $t_{½}\beta$ values of metabolites are longer in patients with renal failure and concentrations may be higher after long-term administration.

Population pharmacokinetic analysis 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; therefore, the predicted time to 90% T_1 suppression may be slightly slower in patients with renal dysfunction. There was no clinically significant alteration in the recovery profile of cisatracurium in patients with renal dysfunction.

Other Patient Factors

The use of inhalation anesthesia (i.e., enflurane or isoflurane) was associated with statistically significant effects on the pharmacokinetics and pharmacodynamics of cisatracurium. These changes were associated with a slightly faster predicted time to 90% suppression for patients under inhalation anesthesia, but there were no clinically significant alterations in the predicted recovery profile of cisatracurium.

STORAGE AND STABILITY

AJ-CISATRACURIUM slowly loses potency with time at a rate of approximately 5% per year under refrigeration (5°C). AJ-CISATRACURIUM should be stored under refrigeration (2° to 8°C) and protected from light to preserve potency. PROTECT FROM FREEZING.

The rate of loss in potency increases to approximately 5% per month at 25°C. If removed from refrigeration to room temperature storage (25°C), AJ-CISATRACURIUM must be used within 21 days, even if re-refrigerated.

Dilution Stability

AJ-CISATRACURIUM diluted to 0.1 mg/mL in 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose and 0.9% Sodium Chloride Injection USP, may be stored either under refrigeration or at room temperature for 24 hours without significant loss of potency. Dilutions to 0.1 mg/mL in 5% Dextrose and Lactated Ringer's Injection may be stored under refrigeration for 24 hours.

AJ-CISATRACURIUM should not be diluted in Lactated Ringer's Injection USP due to chemical instability.

SPECIAL HANDLING INSTRUCTIONS

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AJ-CISATRACURIUM is a colorless to slightly yellow or greenish-yellow solution containing 2 mg cisatracurium (as 2.676 mg cisatracurium besylate) per mL in 10 mL multiple dose vials for injection or infusion. AJ-CISATRACURIUM is supplied in cartons of 10 vials each.

Listing of Non-Medicinal Ingredients

Each mL of AJ-CISATRACURIUM (multi dose vial), a sterile, non-pyrogenic aqueous solution, contains 2 mg cisatracurium (as 2.676 mg cisatracurium besylate), benzenesulfonic acid, (a pH adjuster), 0.9% benzyl alcohol and water for injection. Since AJ-CISATRACURIUM contains benzyl alcohol; it should not be used in neonates. See **CONTRAINDICATIONS.**

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper name: cisatracurium besylate

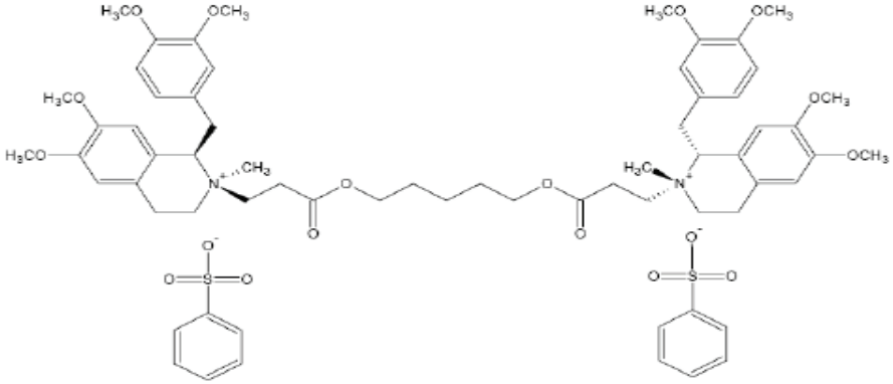
Chemical name: (1R,1'R,2R,2'R)-2,2'-(3,11-dioxo-4,10-dioxatrideca-

[IUPAC]:methylene)bis(1,2,3,4-tetrahydro- 6,7-dimethoxy-2-methyl-1- veratrylisoquinolinium) dibenzenesulfonate

[Chem. Abst.]: {1R-[1,2 (1'R*,2'R*)]}-2,2'-{1,5-pentanediylbis[oxy(3-oxo-3,1- propanediyl)]}bis{1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolinium} dibenzenesulfonate

Molecular formula and molecular mass: $C_{65}H_{82}N_2O_{18}S_2$ 1243.49

Structural formula:



Physicochemical properties:

Cisatracurium besylate is a white to pale yellow powder. The log of the partition coefficient of cisatracurium besylate is –2.12 in a 1-octanol/distilled water system at 25°C. It has a pH of 5.1 for 1% w/v aqueous solution at 22.4°C.

Solubility:

Solvent	Equilibrium Solubility (mg/mL, 25°C)
water	54
0.1 M HCl	55
octan-1-ol	0.4

DETAILED PHARMACOLOGY

In Vitro Studies

Other than the frog isolated nerve muscle preparation, cisatracurium besylate at concentrations up to 10^{-5} M had no significant stimulant or depressant effect on several isolated tissue preparations. In receptor binding assays, $1x10^{-5}$ M cisatracurium had essentially no affinity for the following receptors: adenosine (A_1 and A_2), adrenergic ($alpha_1$, $alpha_2$ and beta), angiotensin II, benzodiazepine, calcium channel (dihydropyridine and phenylalkylamine), calcium release channel (ryanodine), $dopamine_2$, GABA-gated chloride channel (TBPS), glutamate, neurotensin, platelet activating factor, serotonergic ($5HT_{1A}$ and $5HT_2$), and substance P receptors. A weak potency in blocking cholinergic (M_1 and M_2) receptors was observed.

In Vivo Studies

The overall neuromuscular blocking profile of cisatracurium in anesthetized cats, dogs and monkeys is very similar to the neuromuscular blocking profile of atracurium. Spontaneous recovery times from neuromuscular blockade produced by single intravenous bolus injections or infusions were independent of both the administered dose and the duration of blockade, and indicated that cisatracurium was devoid of cumulative effects on the neuromuscular junction. High multiples of the ED_{95} (the effective dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) neuromuscular blocking dose did not produce a correspondingly long duration of action. Like other non-depolarizing neuromuscular blocking agents (e.g., atracurium, vecuronium, mivacurium, doxacurium, d-tubocurarine), the *in vivo* and *in vitro* effects of cisatracurium on the neuromuscular junction were reversed by the acetylcholinesterase inhibitor neostigmine.

Bolus intravenous administration of cisatracurium besylate at doses that produced clinically useful levels of neuromuscular blockade had no effects on sympathetic efferent pathways and had no vagolytic action. There was at least a fifteen-fold separation between the ED_{95} neuromuscular blocking dose and doses that produced transient inhibition of the autonomic nervous system.

The cardiovascular effects of cisatracurium in cats, dogs, and monkeys, at doses that produced complete neuromuscular paralysis, were minimal. Cumulative doses of cisatracurium equivalent to approximately 10 times the ED_{95} decreased mean arterial blood pressure 15% to 20% and had smaller effects on heart rate, cardiac index, total peripheral resistance and left ventricular dP/dt (the change in pressure over the change in time) in anesthetized dogs. Doses of cisatracurium greater than 10 times the ED_{95} produced significantly smaller cardiovascular effects than approximately equal doses of atracurium in anesthetized dogs. In anesthetized cats, cisatracurium, unlike atracurium, did not increase plasma histamine concentrations and did not produce histamine-like cardiovascular effects at high multiples of the ED_{95} neuromuscular blocking dose. Doses of cisatracurium equivalent to 20 to 25 times the ED_{95} neuromuscular blocking dose had minimal (<10%) effects on arterial blood pressure and heart rate in nitrous oxide: oxygen and halothane anesthetized rhesus and cynomolgus monkeys. Significantly, no histamine-like cardiovascular effects were observed after bolus intravenous administration of doses as high as 20 to 25 times the estimated ED_{95} neuromuscular blocking dose in monkeys.

Pharmacokinetics

The pharmacokinetics of cisatracurium was studied in cats (0.25 mg/kg intravenous), dogs (1.0 and 2.0 mg/kg intravenous) and monkeys (1.875 and 3.75 mg/kg intravenous) (see **Table 8**).

Table 8 Pharmacokinetics of Cisatracurium in Animals

Parameter	Dose (mg/kg)				
	Cat	Dog		Cynomologus Monkey	
	0.25	1.0	2.0	1.875	3.75
Plasma elimination t½ (min)	9.0	22.6	19.4	18.6	22.6
Plasma clearance (mL/min/kg)	12.2	8.5	7.30	6.9	7.2
Volume of distribution at steady-state (L/kg)	0.125	0.254	0.200	0.153	0.173

Definitions: min = minute; t½ = half life

Metabolism

Metabolic studies in cats and dogs showed that the monoquaternary alcohol metabolite was the major metabolite, suggesting that ester hydrolysis is an important pathway in the elimination of cisatracurium. Both laudanosine, formed via Hofmann elimination, and the acid metabolite were detected in low concentrations.

TOXICOLOGY

Acute Toxicity

In a study conducted with non-respired rats, lethality was observed at a subcutaneous dose of cisatracurium as low as 5.0 mg/kg. Intravenous dosing of non-respired rats revealed drug related clinical signs at 0.1 mg/kg and lethality at 0.2 mg/kg or higher.

Sub-acute Toxicity

Subacute studies were conducted in monkeys and dogs. Cisatracurium besylate was administered intravenously to anesthetized, ventilated monkeys (n=12) and dogs (n=12) twice weekly for three weeks under conditions simulating clinical usage. The doses represented up to 75 and 40 times the human ED_{95} dose for monkeys and dogs, respectively. Observations in these studies included clinical signs, body weights, food consumption (dogs), electrocardiography, ophthalmology, clinical pathology, gross necropsy, organ weights, histopathology and drug plasma assays. There were no deaths or drug-induced toxicity noted in either study**.**

Mutagenicity and Carcinogenicity

Cisatracurium was not found to be mutagenic in the Ames Salmonella assay, a rat bone marrow cytogenic assay, and in vitro human lymphocyte cytogenics assay. No structural or numerical chromosome aberrations were noted in the presence or absence of metabolic activation.

Cisatracurium was tested for its ability to induce mutations at the heterozygous thymidine kinase (tk+/-) locus in the L5178/tk+/- mouse lymphoma assay both in the presence and in the absence of exogenous metabolic activation (rat liver S9). There was a dose-related mutagenic response in the absence of exogenous mammalian metabolic activation at concentrations of 40 mcg/mL and higher. There was minimal evidence of mutagenicity in the presence of metabolic activation at an isolated concentration of 300mcg/mL. It is unlikely that these mutagenicity results indicate any significant risk with therapeutic use of cisatracurium in humans.

Reproduction and Teratology

A teratology study was conducted in anesthetized, mechanically respired rats given intravenous doses of cisatracurium at 10 or 20 times the human ED_{95} on days 6 through 15 of the gestational period. There was no evidence of embryotoxicity, fetotoxicity, or teratogenicity.

A second rat teratology study was conducted with cisatracurium at doses up to 10 mg/kg/day via subcutaneous route. Maternal toxicity, including some deaths, were noted in the high dose group. When the dose was reduced to 4.0 mg/kg/day, there were no further indications of maternal toxicity. There was no evidence of embryotoxicity, fetotoxicity, or teratogenicity in this study.

Other Studies

A 5 mg/mL solution of cisatracurium did not flocculate plasma protein nor excessively hemolyze a 50% suspension of type O human erythrocytes when tested at ratios of 1:5 and 1:40 for protein flocculation or 1:7 and 1:35 for hemolysis. The degree of hemolysis seen was essentially equivalent to that noted with sterile water for injection (a known hemolytic agent).

Pigs of Pietrain breeding, susceptible to malignant hyperthermia (MH), were given cisatracurium at doses up to 3 x ED_{95} (2000 mcg/kg) and evaluated for the emergence of MH. None of the pigs developed signs of MH, whereas they all developed MH when challenged with halothane/succinylcholine upon return of the twitch response to baseline.

A solution of cisatracurium besylate was shown to be minimally irritating in beagle dogs when injected either perivenously or intramuscularly, simulating a misdosing situation.

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PART III: CONSUMER INFORMATION

[Pr] AJ-CISATRACURIUM
Cisatracurium Besylate Injection

This leaflet is PART III of a three-part "Product Monograph" published when AJ-CISATRACURIUM was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about AJ-CISATRACURIUM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- AJ-CISATRACURIUM is used for providing muscle relaxation during surgery, or during other medical procedures. AJ-CISATRACURIUM is only used in conjunction with an anesthetic.

What it does:

AJ-CISATRACURIUM belongs to a group of medicines called neuromuscular blockers. It works by blocking the effects of acetylcholine, a chemical involved in muscle contraction. This relaxes muscles in the body before surgery of insertion of a breathing tube.

When it should not be used:

AJ-CISATRACURIUM should not be used in neonates (infants less than 1 month of age) or low birth weight infants. Before surgery, be sure to tell all consulting physicians if you:

- are allergic to cisatracurium besylate;
- are allergic to any other bis-benzylisoquinolinium agents;
- are allergic to benzyl alcohol.

What the medicinal ingredient is:

cisatracurium besylate

What the non-medicinal ingredients are:

AJ-CISATRACURIUM (multiple-dose vials) also contains benzenesulfonic acid, benzyl alcohol, and water for injection.

What dosage forms it comes in:

AJ-CISATRACURIUM is available as an injection in vials of 2 mg/mL (10 mL multiple-dose vial)

WARNINGS AND PRECAUTIONS

Before you use • AJ-CISATRACURIUM talk to your doctor or pharmacist if:

- You have difficulty with intubations
- You are susceptible to malignant hyperthermia
- You have kidney or liver problems
- You are pregnant, plan to become pregnant, or are breast-feeding
- You are taking any prescription or non-prescription medications or herbal medicines
- You are allergic to cisatracurium besylate, other medications or substances (e.g., benzyl alcohol)
- You have muscle weakness or partial paralysis on one side of the body or partial paralysis affecting the lower limbs (e.g., Labert-Eaton syndrome, myasthenia gravis)
- You have an electrolyte disturbance or acid-base imbalance or tissue wasting, or are debilitated
- You have had a burn injury requiring medical treatment

AJ-CISATRACURIUM multiple-does vial contains benzyl alcohol, which could be lethal to neonates (infants less than 1 month of age) and low birth weight infants.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with • AJ-CISATRACURIUM include:

- succinylcholine
- inhalation anesthetics (e.g., isoflurane, enflurane)
- anticonvulsants (e.g., phenytoin, carbamazepine)
- antibiotics (e.g., aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin)
- anti-arrhythmics (e.g., procainamide and quinidine)
- lithium and magnesium salts
- local anesthetics

PROPER USE OF THIS MEDICATION

Usual dose:

AJ-CISATRACURIUM is a medicine that is given by injection. AJ-CISATRACURIUM will be administered by an anesthetist or other trained professional during surgery or other medical procedures. The dosage will vary according to many factors such as body weight, age and the duration of the procedure. It will be given to you once you are anesthetized (lost all awareness) for your surgery or procedure.

Overdose:

- Overdose of AJ-CISATRACURIUM lead to prolonged relaxation of the body's muscles. This can be readily treated; however; this situation is unlikely to occur because AJ-CISATRACURIUM is only administered by an anesthetist or other trained doctor who will closely monitor your progress.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, AJ-CISATRACURIUM can cause uncommon side effects which include flushing, skin rashes, feeling agitated, increased cough, nausea, and vomiting.

After exposure to AJ-CISATRACURIUM, you should contact your physician or anesthesia professional if you have any of the side effects listed in the table below.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/Effect		Talk with your doctor or anesthesia professional		Stop taking drug and call your doctor or pharmacists
		Only if Severe	In all Cases	
Common	Allergic Reactions		☑	
	- Rash		☑	
	- Hives		☑	
	- Swelling of the face, throat, lips		☑	
	- Difficulty breathing		☑	
	- Difficulty swallowing		☑	
	Chills		☑	
	Difficulty Breathing/ Choking		☑	
	Dizziness		☑	
	Elevated Blood Glucose		☑	
	High Blood Pressure		☑	
	Jaundice/ Yellowing of the Eyeballs		☑	
	Low Blood Pressure		☑	
	Rapid Heartbeat		☑	
	Seizures/ Seizure-like activity		☑	
	Severe Itching		☑	
	Slow Heartbeat		☑	
	Sudden fever with stiffness, pain and weakness in muscles		☑	
	Wheezing		☑	

This is not a complete list of side effects. For any unexpected effects while taking AJ-CISATRACURIUM, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found by contacting the sponsor, Agila-Jamp Canada Inc, at 1-866-399-9091.

This leaflet was prepared by Agila Jamp Canada Inc.

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