PRESCRIBING INFORMATION

[Pr] ATRACURIUM BESYLATE INJECTION

10 mg/mL

Intravenous Skeletal Neuromuscular Blocking Agent

Hospira Healthcare Corporation
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Date of Preparation:
June 1, 2007

Control # 114495

PACKAGE INSERT

NAME OF DRUG

ATRACURIUM BESYLATE INJECTION

10 mg/mL

PHARMACOLOGICAL CLASSIFICATION

Intravenous Skeletal Neuromuscular Blocking Agent

PHARMACOLOGY

Atracurium Besylate Injection is a nondepolarizing, intermediate-duration, skeletal neuromuscular blocking agent. Nondepolarizing agents antagonize the neurotransmitter action of acetylcholine by binding competitively to cholinergic receptor sites on the motor endplate. This antagonism is inhibited, and neuromuscular block reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

The duration of neuromuscular blockade produced by Atracurium Besylate Injection is approximately one-third to one-half the duration seen with d-tubocurarine, metocurine and pancuronium at equipotent doses. As with other nondepolarizing neuromuscular blockers, the time to onset of paralysis decreases and the duration of maximum effect increases with increasing atracurium doses.

The pharmacokinetics of Atracurium Besylate Injection in man are essentially linear within the 0.3 to 0.6 mg/kg dose range. The elimination half-life is approximately 20 minutes. The duration of neuromuscular blockade produced by Atracurium Besylate Injection does not correlate with plasma pseudocholinesterase levels and is not altered by the absence of renal function.

INDICATIONS

As an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. It can be used most advantageously if muscle twitch response to peripheral nerve stimulation is monitored.

CONTRAINDICATIONS

In patients known to have a hypersensitivity to it.

WARNINGS

Atracurium Besylate Injection should be used only by those skilled in the management of artificial respiration and only when facilities are instantly available for endotracheal intubation and for providing adequate ventilation of the patient, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or control respiration and anticholinesterase reversal agents should be immediately available. Do not give Atracurium Besylate Injection i.m.

Atracurium Besylate Injection has no known effect on consciousness, pain threshold or cerebration. It should be used only with adequate anesthesia.

The injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during i.v. infusion through the same needle. In such mixtures, the resultant pH may cause inactivation of the drug and precipitation of the free acid.

Atracurium Besylate Injection 10 mL multiple-dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal.
The 5 mL vials do not contain benzyl alcohol.

PRECAUTIONS

Histamine Release: The possibility of substantial histamine release with consequent bronchospasm or anaphylaxis in sensitive individuals must be considered. Special caution should be exercised in administering Atracurium Besylate Injection to those patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over 1 minute. Limited clinical experience indicates that mean arterial pressure decreases in a substantial percentage of patients with a history of cardiovascular disease even at these doses.

Pregnancy: Atracurium Besylate Injection has been shown to be potentially teratogenic at up to half the human dose when given to nonventilated rabbits by the s.c. route at sub-paralyzing doses. Therefore, Atracurium Besylate Injection should not be used during pregnancy unless, in the opinion of the physician, the potential benefits outweigh the unknown hazards.

Obstetrics: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that a forceps delivery will be necessary may increase.

In an open study, Atracurium Besylate Injection has been administered (0.3 mg/kg) to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to the drug in any of the newborn infants, although small amounts were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and

Atracurium Besylate Injection dose should be lowered as indicated.

Lactation: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Atracurium Besylate Injection is administered to a nursing woman.

Patients with Special Disease and Conditions: Atracurium Besylate Injection may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders of carcinomatosis.

The safety of Atracurium Besylate Injection has not been established in patients with bronchial asthma.

Obesity: Ideal body weight should be considered in dosage calculations for obese patients with appropriate attention to the attendant risk of underdosing. Severe obesity may pose airway or ventilatory problems before, during, or after the use of nondepolarizing neuromuscular blockers.

Hypothermia: Hypothermia (25 to 28^0C) has been associated with a decreased requirement for nondepolarizing blocking agents.

Cardiovascular Effects: Since Atracurium Besylate Injection has no clinically significant effects on heart rate at the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation.

Malignant Hyperthermia: Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic

triggering agents in MH susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Atracurium Besylate Injection has been used. In a clinical study of MH susceptible patients, Atracurium Besylate Injection did not trigger this syndrome.

Burns: Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.

Electrolyte Abnormalities: Electrolyte abnormalities may antagonize or potentiate the action of neuromuscular blocking agents. For example, hyperkalemia has been reported to antagonize nondepolarizing agents, while hypokalemia has been associated with an enhancement of their activity.

The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Long-Term Use in Intensive Care Unit (ICU): There is only limited information available on the efficacy and safety of long-term (days to weeks) i.v. Atracurium Besylate Injection infusion to facilitate mechanical ventilation in the ICU. These data suggest that dosage requirements show wide interpatient variability and may decrease or increase with time. When there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered.

Little information is available on the plasma levels or clinical consequences of Atracurium Besylate Injection metabolites that may accumulate during days to weeks of Atracurium Besylate Injection administration in ICU patients. Laudanosine, a major biologically active metabolite of Atracurium Besylate Injection without neuromuscular blocking activity, produces transient hypotension and, in higher doses, cerebral excitatory effects (generalized muscle twitching and seizures) when administered to several species of animals. There have been rare reports of seizures in ICU patients

who have received Atracurium Besylate Injection or other agents. These patients usually had predisposing causes (such as head trauma, cerebral edema, hypoxic encephalopathy, viral encephalitis, uremia). There are insufficient data to determine whether or not laudanosine contributes to seizures in ICU patients.

Whenever the use of Atracurium Besylate Injection or any neuromuscular blocking agent is contemplated in the ICU, it is recommended that neuromuscular transmission be monitored continuously during administration with the help of a nerve stimulator. Additional doses of Atracurium Besylate Injection or any other neuromuscular blocking agent should not be given before there is a definite response to T_1 or the first twitch. If no response is elicited, infusion administration should be discontinued until a response returns.

The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of Atracurium Besylate Injection and its metabolites are unknown.

DRUG INTERACTIONS

Atracurium Besylate Injection is potentiated by isoflurane and by enflurane anesthesia, and marginally potentiated by halothane (see Dosage).

Drugs which may enhance the neuromuscular blocking action of Atracurium Besylate Injection include: certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Atracurium Besylate Injection. Atracurium Besylate Injection should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

ADVERSE EFFECTS

Atracurium Besylate Injection was well tolerated and produced few adverse reactions during extensive clinical trials and as observed in clinical practice. Most adverse reactions were suggestive of histamine release. Fully developed anaphylactic or anaphylactoid reactions have been reported, and in rare instances these were severe (e.g. cardiac arrest). Skin flush and decreases in mean arterial pressure were the most common reactions seen in the recommended dose range. The incidences of decreases in mean arterial pressure were substantially increased in patients with a history of cardiovascular disease.

Observed in Controlled Clinical Studies: In 27 studies including 875 patients, Atracurium Besylate Injection was discontinued in 1 patient (who required treatment for bronchial secretions). Six other patients required treatment for adverse reactions attributable to the drug (wheezing in 1, hypotension in 5). Of the 5 patients who required treatment for hypotension, three had a history of significant cardiovascular disease. The overall incidence rate for clinically important adverse reactions, therefore, was 7 in 875 or 0.8%. Table I includes all adverse reactions reported attributable to Atracurium Besylate Injection during clinical trials with 875 patients.

TABLE I

% of Patients Reporting Adverse Reactions

	Initial Dose (mg/kg) (Total = 875 Patients)			
Adverse Reaction	**0.00-0.30 n=485**	**0.31-0.40 n=236**	**0.46-0.50 n=127**	**≥0.56 n=27**
Skin Flush	0.8	5.5	15.0	26.0
Erythema	0.4	0.0	2.4	0.0
Itching	0.4	0.0	0.0	0.0
Wheezing/ Bronchial Secretions	0.2	0.0	0.8	0.0
Hives	0.2	0.0	0.0	0.0

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Table II summarizes the incidences of substantial vital sign changes noted during Atracurium Besylate Injection clinical trials with 530 patients in whom these parameters were assessed.

TABLE II

% of Patients with Vital Sign Changes (ASA 1 and 2)*

		Initial Dose (mg/kg)			
Vital Sign Change		**0.00-0.30 n=365**	**0.36-0.40 n=124**	**0.50 n=20**	**≥0.60 n=21**
Mean Arterial Pressure					
Decrease	≥40	0.3	0.0	10.0	5.0
Decrease	≥30	1.1	0.0	15.0	15.0
Decrease	≥20	2.5	2.4	15.0	30.0
Increase	≥20	7.4	7.3	5.0	0.0
Increase	≥30	1.9	3.2	0.0	0.0
Increase	≥40	0.8	1.6	0.0	0.0
Heart Rate					
Decrease	≥40	0.3	0.0	0.0	0.0
Decrease	≥30	0.8	0.0	0.0	0.0
Decrease	≥20	3.0	1.6	0.0	5.0
Increase	≥20	4.9	4.0	5.0	10.0
Increase	≥30	1.6	2.4	5.0	5.0
Increase	≥40	1.4	1.6	0.0	0.0

* American Society of Anesthesiologists Classification of Physical Status:
1. A normal healthy patient.
2. A patient with a mild systemic disease

In a small group of patients with cardiovascular disease (n=34) the changes in vital signs were more predominant, even at the lower doses. (see Table III).

TABLE III

Patients with Cardiovascular Disease with Vital Sign Changes (%)

Vital Sign Change		Initial Dose (mg/kg) 0.00-0.30 n=18	0.36-0.40 n=16
Mean Arterial Pressure			
Decrease	≥40	0.0	1 (6.3)
Decrease	≥30	2 (11.1)	6 (37.5
Decrease	≥20	7 (38.9)	11 (68.8)
Increase	≥20	0.0	2 (12.5)
Increase	≥30	0.0	0.0
Heart Rate			
Decrease	≥30	0.0	0.0
Decrease	≥20	2 (11.0)	1 (6.3)
Increase	≥20	2 (11.0)	0.0
Increase	≥30	0.0	0.0

Three large prospective postmarketing surveillance studies have been reported, tabulating the incidence of adverse reactions associated with Atracurium Besylate Injection; they did not uncover any new events attributable to the drug.

Observed in Clinical Practice: Based on initial clinical practice experience in approximately 11 million patients who received Atracurium Besylate Injection, spontaneously reported adverse reactions were uncommon (0.006%). The following adverse reactions are among the most frequently reported, but there are insufficient data to support an estimate of their incidence.

General: Allergic reactions (anaphylactic or anaphylactoid responses) which, in rare instances, were severe (e.g. cardiac arrest).

Musculoskeletal: Inadequate block, prolonged block.

Cardiovascular: Hypotension, vasodilation (flushing), tachycardia, bradycardia.

Respiratory: Dyspnea, bronchospasm, laryngospasm.

Integumentary: Rash, urticaria, reaction at injection site.

There have been rare reports of seizures in ICU patients following long-term infusion of Atracurium Besylate Injection to support mechanical ventilation. There are insufficient data to define the contribution, if any, of Atracurium Besylate Injection and/or its metabolite laudanosine. (see Precautions: Long-Term Use in the Intensive Care Unit).

OVERDOSE

Symptoms and Treatment: There has been limited experience with Atracurium Besylate Injection overdosage. The possibility of limited iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses can be expected to produce enhanced pharmacological effects. Overdosage may increase the risk of histamine release and cardiovascular effects, especially hypotension. If cardiovascular support is necessary, this should include proper positioning, fluid administration, and the use of vasopressor agents if necessary. The patient's airway should be assured, with manual or mechanical ventilation maintained as necessary. A longer duration of neuromuscular blockade may result from overdosage and a peripheral nerve stimulator should be used to monitor recovery. Recovery may be facilitated by administration of an anticholinesterase-reversing agent such as neostigmine, edrophonium, or pyridostigmine, in conjunction with an anticholinergic agent such as atropine or glycopyrrolate.

Three pediatric patients (3 weeks, 4 and 5 months of age) unintentionally received doses of 0.8 mg/kg to 1 mg/kg of Atracurium Besylate Injection. The time to 25% recovery (50 to 55 minutes) following these doses, which were 5 to 6 times the ED_{95} dose, was moderately longer than the corresponding time observed following doses 2 to 2.5 times the Atracurium Besylate Injection ED_{95} dose in infants (22 to 36 minutes). Cardiovascular changes were minimal. Nonetheless, the possibility of cardiovascular changes must be considered in the case of overdose.

An adult patient (17 years of age) unintentionally received an initial dose of 1.3 mg/kg of Atracurium Besylate Injection. The time from injection to 25% recovery (83 minutes) was approximately twice that observed following maximum recommended doses in adults (35 to 45 minutes). The patient experienced moderate hemodynamic changes (13% increase in mean arterial pressure and 27% increase in heart rate) which persisted for 40 minutes and did not require treatment.

DOSAGE

To avoid distress to the patient, Atracurium Besylate Injection should not be administered before unconsciousness has been induced. It should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g. barbiturate solutions).

Atracurium Besylate Injection should be administered i.v. **Do not give Atracurium Besylate Injection i.m.** I.M. administration may result in tissue irritation and there are no clinical data to support this route of administration.

The use of a peripheral nerve stimulator to monitor muscle twitch suppression and recovery will permit the most advantageous use of the drug and minimize the possibility of overdosage.

Bolus Injection for Intubation and Maintenance of neuromuscular Blockade:

Adults: A dose of 0.4 to 0.5 mg/kg (1.7 to 2.2 times the ED_{95}), given as an i.v. bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade being achieved approximately 3 to 5 minutes after injection. Clinically effective neuromuscular blockade generally lasts to 20 to 35 minutes under balanced anesthesia. Recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete 60 minutes after injection.

Atracurium Besylate Injection is potentiated by isoflurane or enflurane anesthesia. The same initial dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation

agents; however, if Atracurium Besylate Injection is first administered under steady state isoflurane or enflurane anesthesia, the initial dose may be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg, to adjust for the potentiating effects of these anesthetic agents. With halothane, which has only a marginal (approximately 20%) potentiating effect on Atracurium Besylate Injection, smaller dosage reductions may be considered.

Doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Atracurium Besylate Injection injection, but the need for maintenance doses should be determined by clinical criteria. Because Atracurium Besylate Injection lacks cumulative effects, maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane. Higher doses (up to 0.2 mg/kg) permit maintenance dosing at longer intervals.

Children: No dosage adjustments are required for pediatric patients 2 years of age or older. A dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in children than in adults.

Reversal: Reversal of neuromuscular blockade produced by Atracurium Besylate Injection can be achieved with an anticholinesterase agent such as neostigmine, edrophonium, or pyridostigmine, in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. Under balanced anesthesia, reversal can usually be attempted approximately 20 to 35 minutes after an initial dose of. 0.4 to 0.5 mg/kg, or approximately 10 to 30 minutes after a 0.08 to 0.10 mg/kg maintenance dose, when recovery of muscle twitch has started. Complete reversal is usually accomplished within 8 to 10 minutes of the administration of reversing agents. Rare incidences of breathing difficulties, possibly related to incomplete reversal have been reported following attempted pharmacologic antagonism of Atracurium Besylate Injection-induced neuromuscular blockade. As with other agents in this class, the tendency for residual neuromuscular block is increased if reversal is attempted at deep levels of blockade or if inadequate doses of reversal agents are employed.

Special Considerations: An initial dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over

1 minute, is recommended for adults or children with significant cardiovascular disease (an increased incidence of hypotensive episodes has been seen in these patients) and for adults or children with any history (e.g. several anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. There has been no clinical experience with Atracurium Besylate Injection in these patients, and no specific dosage adjustments can be recommended.

No Atracurium Besylate Injection dosage adjustments are required for patients with renal disease.

An initial dose of 0.3 to 0.4 mg/kg is recommended for adults following the use of succinylcholine for intubation under balanced anesthesia. Further reductions may be desirable with the use of potent inhalation anesthetics. The patient should be permitted to recover from the effects of succinylcholine prior to Atracurium Besylate Injection administration. Insufficient data are available for recommendation of a specific initial Atracurium Besylate Injection dose for administration following the use of succinylcholine in children and infants.

As with other parenteral drug products, Atracurium Besylate Injection should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Use by Infusion: After administration of a recommended initial bolus dose of Atracurium Besylate Injection (0.3 to 0.5 mg/kg), a diluted solution can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular blockade during extended surgical procedures.

Long-term i.v. infusion to support mechanical ventilation in the intensive care unit has not been

studied sufficiently to support dosage recommendations (see Precautions: Long-Term Use in Intensive Care Unit).

Infusion 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 pump.

Infusion should be initiated only after evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 μg/kg/minute may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 μg/kg/minute should be adequate to maintain continuous neuromuscular blockade in the range of 89 to 99% in most pediatric and adult patients under balanced anesthesia. Occasional patients may require infusion rates as low as 2 μg/kg/minute or as high as 15 μg/kg/minute.

The neuromuscular blocking effect of Atracurium Besylate Injection administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of Atracurium Besylate Injection should, therefore, be considered for patients receiving inhalation anesthesia. The rate of infusion should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane anesthesia; smaller reductions should be considered in the presence of halothane.

In patients undergoing cardiopulmonary bypass with induces hypothermia, the rate of infusion required to maintain adequate surgical relaxation during hypothermia (25 to 28^{0}C) has been shown to be approximately half the rate required during normothermia.

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

The amount of infusion solution required per minute will depend upon the concentration of

Atracurium Besylate Injection in the infusion solution, the desired dose and the patient's weight. Tables IV and V provide guidelines for delivery in mL/hour (equivalent to microdrops/minute when 60 microdrops = 1 mL) of drug solutions in concentrations of 0.2 mg/mL (20 mg in 100 mL) or 0.5 mg/mL (50 mg in 100 mL) with an infusion pump or a gravity flow device.

TABLE IV

Atracurium Besylate Infusion Rates for a Concentration of 0.2 mg/mL

	Drug Delivery Rate (µg/kg/min)					
Patient Weight (kg)	**5**	**6**	**7**	**8**	**9**	**10**
	Infusion Delivery Rate (mL/hr)					
30	45	54	63	72	81	90
35	53	63	74	84	95	105
40	60	72	84	96	108	120
45	68	81	95	108	122	135
50	75	90	105	120	135	150
55	83	99	116	132	149	165
60	90	108	126	144	162	180
65	98	117	137	156	176	195
70	105	126	147	168	189	210
75	113	135	158	180	203	225
80	120	144	168	192	216	240
90	135	162	189	216	243	270
100	150	180	210	240	270	300

TABLE V

Atracurium Besylate Infusion Rates for a Concentration of 0.5 mg/mL						
	Drug Delivery Rate (µg/kg/min)					
Patient Weight (kg)	**5**	**6**	**7**	**8**	**9**	**10**
	Infusion Delivery Rate (mL/hr)					
30	18	22	25	29	32	36
35	21	25	29	34	38	42
40	24	29	34	38	43	48
45	27	32	38	43	49	54
50	30	36	42	48	54	60
55	33	40	46	53	59	66
60	36	43	50	58	65	72
65	39	47	55	62	70	78
70	42	50	59	67	76	84
75	45	54	63	72	81	90
80	48	58	67	77	86	96
90	54	65	76	86	97	108
100	60	72	84	96	108	120

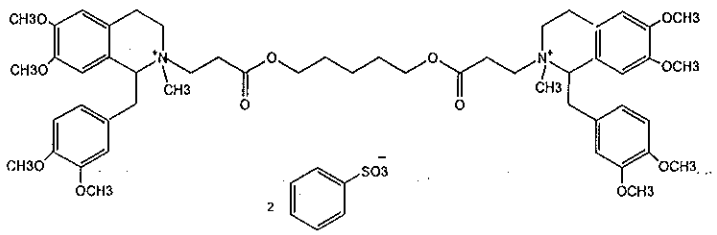
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Atracurium besylate

Chemical Name: 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-methylisoquino-linium] dibenzenesulfonate

Chemical Structure



Molecular Formula: $C_{65}H_{82}N_2O_{18}S_2$

Molecular Weight: 1243.51

Description:

Atracurium besylate is a complex molecule containing four sites at which different stereochemical configurations can occur. The symmetry of the molecule, however, results in only ten instead of sixteen possible different isomers. The manufacture of atracurium besylate results in these isomers being produced in unequal amounts but with a consistent ratio. Those molecules in which the methyl group attached to the quaternary nitrogen projects on the opposite side to the adjacent substituted benzyl moiety predominate by approximately 3:1.

Atracurium besylate is a white to pale yellow powder. It is freely soluble in acetonitrile and in chloroform, soluble in water, and practically insoluble in diethyl ether. Melting point is 85-90°.

Composition:

Atracurium Besylate Injection is a sterile, non-pyrogenic aqueous solution. Each mL contains 10 mg atracurium besylate. The pH is adjusted to 3.25 to 3.65 with benzenesulfonic acid. The multiple-dose vial contains 0.9% w/v benzyl alcohol added as a preservative.

STABILITY AND STORAGE RECOMMENDATIONS

Atracurium Besylate Injection slowly loses potency with time at the rate of approximately 6% per year under refrigeration (2 to 8^{0}C). The injection **should be stored under refrigeration (2 to 8^{0}C)** to preserve potency. **Protect from freezing.**

Compatibility and Admixtures: Infusion solutions may be prepared by admixing Atracurium Besylate Injection with an appropriate diluent such as 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose and 0.9% Sodium Chloride Injection USP. Solutions containing 0.2 mg/mL or 0.5 mg/mL atracurium in these diluents may be stored either under refrigeration or at room temperature for 24 hours without significant loss of potency. Infusion solutions should be used within 24 hours of preparation. Unused solutions should be discarded.

In Lactated Ringer's Injection minor degradation was observed at room temperature. However, the product is stable at 2-8^{0}C, protected from light for 24 hours.

Care should be taken during admixture to prevent inadvertent contamination. As with other parenteral drug products, the admixtures should be inspected visually for discoloration, haziness, particulate matter and leakage prior to administration, whenever a solution and container permit. Discard unused portions.

AVAILABILITY OF DOSAGE FORMS

Single-Dose Vials: Each mL of sterile, non-pyrogenic aqueous solution contains: atracurium besylate 10 mg. pH adjusted to 3.25 to 3.65 with benzene sulfonic acid. Vials of 5 mL.

Multi-Dose Vials: Each mL of sterile, non-pyrogenic aqueous solution contains: atracurium besylate 10 mg. Non-medicinal ingredients: benzyl alcohol 0.9% w/v (preservative). pH adjusted to 3.25 to 3.65 with benzene sulfonic acid. Multiple-dose vials of 10 mL.

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