SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:

1.1 Product Name:

ARTACIL (ATRACURIUM BESYLATE INJECTION USP)

1.2 Strength (Composition):

10 mg / ml – 2.5 ml

1.3 Pharmaceutical dosage form:

Solution for Injection

2. Qualitative and Quantitative composition:

Sr. No.	Particulars	Grade	Qty. / ml	O.A. %	Function
01.	Atracurium Besylate	USP	10 mg	12.5%	Active

For full list of excipients see section 6.1

3. Pharmaceutical form:

A clear colourless solution.

4. Clinical Particulars:

4.1 Therapeutic indications:

1. Atracurium Besylate is indicated as an adjunct to anesthesia to relax the skeletal muscles during a wide range of surgical procedures and to facilitate controlled ventilation of the lungs.

2. To facilitate endotracheal intubation where subsequent maintenance of neuromuscular relaxation is required.

3. In intensive care to facilitate ventilation.

4.2 Posology and method of administration:

DO NOT GIVE ATRACURIUM BESYLATE BY INTRAMUSCULAR ADMINISTRATION.

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

Intramuscular administration of atracurium besylate may result in tissue irritation and there are no clinical data to support this route of administration. As with other neuromuscular blocking agents, the use of a peripheral nerve stimulator will permit the most advantageous use of atracurium besylate, minimizing the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Adults :

An atracurium besylate dose of 0.4 to 0.5 mg / kg (1.7 to 2.2 times the ED), given as an intravenous 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 block achieved approximately 3 to 5 minutes after injection. Clinically required neuromuscular block generally lasts 20 to 35 minutes under balanced anesthesia. Under balanced anesthesia, recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Atracurium is potentiated by isoflurane or enflurane anesthesia.

The same initial atracurium besylate dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if atracurium is first administered under steady-state of isoflurane or enflurane, the initial atracurium besylate dose should 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, smaller dosage reductions may be considered.

Atracurium besylate doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular block during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial atracurium besylate injection, but the need for maintenance doses should be determined by clinical criteria. Because atracurium 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 atracurium doses (up to 0.2 mg/kg) permit maintenance dosing at longer intervals.

Pediatric Patients :

No atracurium dosage adjustments are required for pediatric patients two years of age or older. An atracurium besylate 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 infants and children than in adults.

Use of infusion in the operating room :

After administration of a recommended initial bolus dose of atracurium besylate injection (0.3 to 0.5 mg/kg), a diluted solution of atracurium besylate can be administered by continuous infusion to adults and pediatric patients aged 2 or more years for maintenance of neuromuscular block during extended surgical procedures.

Infusion of atracurium 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 atracurium should be initiated only after early evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 mcg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 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 balanced anesthesia. Occasional patients may require infusion rates as low as 2

mcg / kg / min or as high as 15mcg/kg/min. The neuromuscular blocking effect of atracurium administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of atracurium should, therefore, be considered for patients receiving inhalation anesthesia. The rate of atracurium 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 induced hypothermia, the rate of infusion of atracurium required to maintain adequate surgical relaxation during hypothermia (25° to 28°C) has been shown to be approximately half the rate

required during normothermia. Spontaneous recovery from neuromuscular block following discontinuation of atracurium infusion may be expected to proceed at a rate comparable

to that following administration of a single bolus dose.

Infusion in the Intensive Care Unit (ICU) :

The principles for infusion of atracurium in the OR are also applicable to use in the ICU. An infusion rate of 11 to 13 mcg/kg/min (range: 4.5 to 29.5) should provide adequate neuromuscular block in adult patients in an ICU. Limited information suggests that infusion rates required for pediatric patients in the ICU may be higher than in adult patients.

COMPATIBILITY AND ADMIXTURES

Infusion solutions of Atracurium Besylate may be prepared by admixing Atracurium Besylate Injection with an appropriate diluent like 5% w/v Dextrose injection, 0.9% w/ v NaCl or 5% w/v dextrose and 0.9% w/v NaCl injection. Infusion solutions should be used within 24 hours of preparation unused solution should be discarded. Solutions containing 0.2 mg/ml or 0.5 mg / ml Atracurium Besylate in the above diluents may be stored either under

refrigeration or at room temperature for 24 hours without significant loss of potency. Care should be taken to prevent inadvertent contamination during

admixture. Visually inspect prior to administration. Spontaneous degradation of Atracurium Besylate occurs more rapidly in lactated Ringer's solution then in 0.9% w/

v NaCl. Hence lactated Ringer's solution should not be used as a diluent in preparing an infusion solution of Atracurium.

4.3 Contra-indications:

Atracurium Besylate should not be administered to patients known to have a hypersensitivity to it.

4.4 Special warning and Special precautions for use: Warnings

KEEP OUT OF REACH OF CHILDREN.

Like all other neuromuscular blocking agents, atracurium besylate paralyses the respiratory muscle as well as other skeletal muscles but has no effect on consciousness. Hence, atracurium besylate should be administered only with adequate general anaesthesia and only by those skilled in airway management and respiratory support.

Equipment and personnel must be immediately available for endotracheal intubation and support of ventilation. Anticholinesterase reversal agents should be immediately available. Do not give atracurium besylate by intramuscular route. Atracurium besylate injection, which has an acid ph, should not be mixed with alkaline solutions in the same syringe or administered simultaneously during iv infusion through the same needle depending on the resultant ph of such mixtures, atracurium besylate may be inactivated and a free acid may be precipitated.

Precautions

General: Although Atracurium Besylate is a less potent histamine releaser than dtubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered.

Special cautions: Like in case of other neuromuscular blocking agents, caution should be exercised in administering Atracurium Besylate to patients in whom substantial

histamine release would be especially hazardous (i.e. patients with clinically significant cardiovascular disease) and in patients with any history (i.e. severe

anaphylactic reaction or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial dose of Atracurium Besylate is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Atracurium Besylate may have profound effect in patients with myasthenia gravis, Eaton - Lambert syndrome, or other neuromuscular disease in which potentiation of NDBAs has been noted. Resistance to NDBAs may develop in burn patients, thereby needing increase doses of the same. When a small vein is selected as the injection

sight, Atracurium Besylate should be flushed through the vein with physiological saline after injection. When other anaesthetic agents are administered through the same in - dwelling needle or cannula as Atracurium Besylate, it is important that each drug is flushed through with an adequate volume of physiological saline. Atracurium Besylate is hypnotic and must not be administered into the infusion line of a blood transfusion.

In contrast to other competitive neuromuscular blockers, reduction in body temperature may necessitate a dosage reduction of Atracurium Besylate since cooling reduces the rate of inactivation of Atracurium Besylate, but physiological variations in body temperature and pH will not affect their action.

4.5 Interaction:

The neuromuscular block produced by Atracurium Besylate may be increased by the concomitant use of volatile anaesthetic agents like Halothane, Isoflurane and Enflurane. Like all non-depolarising neuromuscular blocking agents (NDNBA), the magnitude and/ or duration of the block may be increased as a result of interactions with:-

1. Antibiotics, including Aminoglycosides, Polymyxins, Spectinomycin, Tetracyclines, Lincomycin and Clindamycin.
2. Antiarrhythmic drugs - Propranalol, Calcium channel blockers, Lignocaine and Quinidine.
3. Diuretics like Frusemide
4. Magnesium Sulfate

5. Ketamine
6. Lithium salts
7. Ganglion blocking agents like Trimetaphan.
8. Succinyl Choline. Prior administration of Succinyl Choline 1mg/kg IV, enhances the magnitude of twitch response suppression. However, it should not be administered to prolonged the neuromuscular blocking effect of Atracurium as this may result in prolonged and complex blocked which can be difficult to reverse with

anticholinesterase drugs.

4.6 Pregnancy and lactation:

Pregnancy Category C: Atracurium besylate has

been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Atracurium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: 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 forceps delivery will be necessary may increase.

In patients receiving magnesium sulfate, the reversal of neuromuscular block may be unsatisfactory and the dose of atracurium besylate should be lowered as indicated.

Nursing Mothers : 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 is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 1 month have not been established.

4.7 Effects on ability to drive and operate machine:

It is not recommended to use potentially dangerous machinery or drive a car within 24 hours after full recovery from the neuromuscular blocking action of atracurium.

4.8 Undesirable effects: ADVERSE REACTIONS

Associated with the use of Atracurium Besylate, there have been reports of skin flushing, mild transient hypotension or bronchospasms, which have been attributed to histamine release. Very rarely, severe anaphylactic reactions have been reported in patients receiving Atracurium Besylate. There have been rare reports of seizures in I.C.U. patients who have been receiving Atracurium concurrently with several other agents. There

have been some reports of muscle weakness and /or myopathy following prolong use of muscle relaxants in severely ill patients in the I.C.U.

4.9 Overdoses:

There has been limited experience with overdosage of atracurium besylate. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of atracurium 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 block 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.

The appropriate package inserts should be consulted for prescribing information.

5. Pharmacological properties:

5.1 Pharmacodynamic Properties:

Atracurium besylate is a nondepolarizing skeletal muscle relaxant. Nondepolarizing agents antagonize the neurotransmitter action of acetylcholine by binding competitively with cholinergic receptor sites on the motor end-plate. This antagonism is inhibited and neuromuscular block reversed, by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Atracurium can be used most advantageously if muscle twitch response to peripheral nerve stimulation is monitored to assess degree

of muscle relaxation. The duration of neuromuscular block produced by atracurium is approximately one-third to one-half the duration of block by d-tubocurarine, metocurine, and pancuronium at initially 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. Complete reversal is usually attained within 8 to 10 minutes of the administration of reversing agents. Rare instances of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacologic antagonism of atracurium-induced neuromuscular block. As with other agents in this class, the tendency for residual neuromuscular block is increased if reversal is attempted at deep levels of block or if inadequate doses of reversal agents are employed.

5.2 Pharmacokinetic Properties:

The pharmacokinetics of atracurium

in humans 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 BLOCK PRODUCED BY ATRACURIUM BESYLATE DOES NOT CORRELATE WITH PLASMA PSEUDOCHOLINESTERASE LEVELS AND IS NOT ALTERED

BY THE ABSENCE OF RENAL FUNCTION. This is consistent with the results of in vitro studies which have shown that atracurium is inactivated in plasma via two nonoxidative pathways: ester hydrolysis, catalyzed by nonspecific esterases; and Hofmann elimination, a nonenzymatic chemical process which occurs at physiological pH. Some placental transfer occurs in humans. Radiolabel studies demonstrated that atracurium undergoes extensive degradation in cats, and that 95 neither kidney nor liver plays a major role in this elimination. The metabolites in bile and urine were similar, including products of Hofmann elimination and ester hydrolysis. Elderly patients may

have slightly altered pharmacokinetic parameters compared to younger patients, with a slightly decreased total plasma clearance which is offset by a corresponding increase in volume of distribution. The net effect is that there has been no significant difference in clinical duration and recovery from neuromuscular block observed between elderly and younger patients receiving atracurium besylate.

Atracurium is a less potent histamine releaser than d-tubocurarine or metocurine. Histamine release is minimal with initial atracurium besylate doses up to 0.5 mg/kg, and hemodynamic changes are minimal within the recommended dose range. A moderate histamine release and significant falls in blood pressure have been seen following 0.6 mg/kg of atracurium besylate. The histamine and hemodynamic responses were poorly correlated. The effects were generally short-lived and manageable, but

the possibility of substantial histamine release in sensitive individuals or in patients in whom substantial histamine release would be especially hazardous (e.g., patients with significant cardiovascular disease) must be considered. It is not known whether the prior use of other nondepolarizing neuromuscular blocking agents has any effect on the activity of atracurium. The prior use of succinylcholine decreases by approximately

2 to 3 minutes the time to maximum block induced by atracurium besylate, and may increase the depth of block. Atracurium should be administered only after a patient recovers from succinylcholine-induced neuromuscular block.

5.3 Preclinical Safety Data:

Carcinogenicity / Mutagenicity: Carcinogenicity studies have not been performed. Atracurium yielded negative results for gene mutation in bacteria, and chromosomal damage in bone marrow of rats. A positive response in the mouse lymphoma assay was observed only at highly cytotoxic concentrations. This single positive response is not considered to be of clinical relevance.

Reproductive toxicity: Animal studies have indicated that atracurium has no adverse effect on foetal development.

6. Pharmaceutical particulars:

6.1 List of excipients: Benzene Sulphonic Acid Water for InjectionsUSP

6.2 Incompatibilities:

Atracurium Besilate Solution for Injection has an acid pH and therefore should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle.

6.3 Shelf – life:

18 Months

6.4 Special precautions for storage:

Store between 2°C and 8°C., protected from light. Do not freeze.

6.5 Nature and contents of container:

3 ml flint ampoule black OPC dotted, such one ampoule packed in a blister pack, such 5 blister pack packed in a carton along with package insert.

6.6 Special Precautions for Handling and Disposal:

Contains no preservative. Discard residue immediately after use. Do not use if cloudiness or precipitate is observed.

Atracurium besilate infusion solutions may be prepared by admixing Atracurium Besilate Injection with an appropriate diluent (see below) to give an atracurium besilate concentration of 0.5 mg/ml to 5 mg/ml.

7. Marketing authorization holder:

M/s. NEON LABORATORIES LIMITED

140 Damji Shamji Industrial Complex,

28, Mahal Indl. Estate, Mahakali Caves Road, Andheri (East), Mumbai - 400 093, INDIA.

8. Marketing authorization number :-

CTD 1766

9. Date of first authorization/ Renewal of the authorization :----

10. Date of revision of the text: --

December, 2025