SUMMARY PRODUCT CHARACTERISTICS (SmPC)

1 Name of the Finished Product:
ATACURIUM

2 Qualitative and quantitative compositions:
Each ml contains: Atracurium Besylate USP……10 mg
For the full list of excipients, see section 6.1.

3 Pharmaceutical form:
Injection.
A clear, colourless solution.

4 Clinical particulars:

4.1 Therapeutic indications:
Atracurium Besilate solution for injection/infusion is indicated as an adjunct to general anaesthesia during surgery to relax skeletal muscles, and to facilitate endotracheal intubation and mechanical ventilation. It is also indicated to facilitate mechanical ventilation in intensive care unit (ICU) patients. Atracurium Besilate solution for injection/infusion is indicated in adults and in paediatric patients aged over 1 month to 18 years.

4.2 Posology and method of administration
Atracurium Besilate solution for injection/infusion should only be administered by, or under the supervision of, anaesthesiologists or practitioners familiar with the use and action of neuromuscular blocking agents and only when facilities are immediately available for endotracheal intubation and for providing adequate ventilation support, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or control ventilation, and anticholinesterase agents should be immediately available for reversal of neuromuscular blockade.

Posology
Atracurium Besilate solution for injection/infusion should only be administered by intravenous injection/infusion. Do not give Atracurium Besilate solution for injection/infusion intramuscularly since this may result in tissue irritation and there are no clinical data to support this route of administration.

In common with all neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of Atracurium Besilate solution for injection/infusion in order to individualise dosage requirements.
Use as an adjunct to general anaesthesia
To avoid distress to the patient, Atracurium Besilate solution for injection/infusion should not be administered before unconsciousness has been induced.
Initial bolus doses for intubation
An initial Atracurium Besilate solution for injection/infusion dose of 0.3 to 0.6 mg/kg (depending on the duration of full block required), given as an intravenous bolus injection, is recommended. This will provide adequate relaxation for about 15 to 35 minutes.

Endotracheal intubation can usually be accomplished within 90 to 120 seconds of the intravenous injection of 0.5 to 0.6 mg/kg. Maximum neuromuscular blockade is generally achieved approximately 3 to 5 minutes after administration. The recovery index (25% to 75%) is 10 to 15 minutes. Spontaneous recovery from the end of full block occurs in about 35 minutes as measured by the restoration of the tetanic response to 95% of normal neuromuscular function.

Maintenance doses

Intermittent IV injection

During prolonged surgical procedures neuromuscular blockade may be maintained with Atracurium Besilate solution for injection/infusion maintenance doses of 0.1 to 0.2 mg/kg. Successive supplementary dosing does not give rise to accumulation of neuromuscular blocking effect.

Use as an infusion

After the initial Atracurium Besilate solution for injection/infusion bolus dose, neuromuscular blockade may be maintained during prolonged surgical procedures by administering Atracurium Besilate solution for injection/infusion as a continuous intravenous infusion at a rate of 0.3 to 0.6 mg/kg/hour. The infusion should not be commenced until early spontaneous recovery from the initial atracurium bolus dose is evident. After infusion, the recovery index (25% to 75%) is 10 to 15 minutes, which is similar to that observed after intermittent injection.

Atracurium Besilate solution for injection/infusion can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25 °C to 26 °C reduces the rate of inactivation of atracurium, and therefore full neuromuscular block may be maintained with approximately half the original infusion rate at these temperatures.

Facilitation of mechanical ventilation in intensive care unit (ICU) patients

After an optional initial bolus dose of 0.3 to 0.6 mg/kg, neuromuscular block may be maintained by administering a continuous infusion of Atracurium Besilate solution for injection/infusion at rates of between 11 and 13 microgram/kg/min (0.65 to 0.78 mg/kg/hr). There may be wide inter-patient variability in dosage requirements, and these may increase or decrease with time. Infusion rates as low as 4.5 microgram/kg/min (0.27 mg/kg/hr) or as high as 29.5 microgram/kg/min (1.77 mg/kg/hr) are required in some patients.

The rate of spontaneous recovery from neuromuscular block after infusion of Atracurium Besilate solution for injection/infusion in ICU patients is independent of the duration of administration.

Spontaneous recovery to a train-of-four ratio > 0.75 (the ratio of the height of the fourth to the first twitch in a train-of-four) can be expected to occur in approximately 60 minutes. A range of 32 to 108 minutes has been observed in clinical trials.

Reversal of neuromuscular blockade

The neuromuscular blockade induced by atracurium can be reversed with an anticholinesterase agent such as neostigmine or pyridostigmine, usually in conjunction with an anticholinergic agent such as atropine or glycopyrronium to prevent the adverse muscarinic effects of the anticholinesterase. Under balanced

anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after the initial atracurium dose, or approximately 10 to 30 minutes after the last atracurium maintenance dose, when recovery of muscle twitch has started. Complete reversal of neuromuscular blockade is usually achieved within 8 to 10 minutes after administration of the reversing agents.

Rare instances of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacological antagonism of atracurium 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.

Dosage considerations
Use in the elderly

The standard dose of atracurium may be used in elderly patients, however, it is recommended that the initial dose be at the lower end of the range, and it should be administered slowly.

Use in patients with reduced renal and/or hepatic function
Standard dosages may be used at all levels of renal or hepatic function, including endstage failure.

Use in patients with cardiovascular disease
In patients with significant cardiovascular disease the initial dose of atracurium should be administered over a period of at least 60 seconds and the dose should be divided (see section 4.4).

Paediatric population
Use in paediatric patients aged over 1 month

The dosage in paediatric patients over the age of 1 month is similar to that in adults on a body weight basis, however, large individual variability in the neuromuscular response in paediatric patients indicates that neuromuscular monitoring is essential.

Use in neonates
The use of Atracurium solution for injection/infusion is not recommended in neonates since there are insufficient data available (see section 5.1).

Method of administration
For intravenous administration as a bolus injection or as a continuous infusion.

Atracurium Besilate solution for injection/infusion should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g., barbiturate solutions) (see section 4.4).
When a small vein is selected as the injection site, Atracurium solution for injection/infusion should be flushed through the vein with physiological saline

after injection. When other anaesthetic drugs are administered through the same indwelling needle or cannula as Atracurium solution for injection/infusion, it is important that each drug is flushed through with an adequate volume of physiological saline.

See section 6.6 for a list of compatible infusion solutions.

4.3 Contra-indications:

Atracurium is contraindicated in patients known to be hypersensitive to atracurium, cisatracurium or benzenesulfonicacid.

4.4 Special warning and precautions for use:

Precautions: In common with all the other neuromuscular blocking agents, Atacurium paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness. Atacurium should be administered only with adequate general anaesthesia and only by or under the close supervision of an experienced anaesthetist with adequate facilities for endotracheal intubation and artificial ventilation.

The potential for histamine release exists in susceptible patients during Atacurium administration. Caution should be exercised in administering Atacurium to patients with a history suggestive of an increased sensitivity to the effects of histamine. In particular, bronchospasm may occur in patients with a history of allergy and asthma.

High rates of cross-sensitivity between neuromuscular blocking agents have been reported. Therefore, where possible,before administering atracurium, hypersensitivity to other neuromuscular blocking agents should be excluded.

Atracurium should only be used when absolutely essential in susceptible patients. Patients who experience a hypersensitivity reaction under general anaesthesia should be tested subsequently for hypersensitivity to otherneuromuscular blockers.

Monitoring of serial creatinine phosphate (cpk) values should be considered in asthmatic

patients receiving high dose corticosteroids and neuromuscular blocking agents in ICU. Atacurium does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, Atacurium has no clinically significant effects on heart rate in the recommended dosage range and it will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery.

In common with other non-depolarising neuromuscular blocking agents, increased sensitivity to atracurium may be expected in patients with myasthenia gravis and other forms of neuromuscular disease.

As with other neuromuscular blocking agents severe acid-base and/or serum electrolyte abnormalities may increase ordecrease the sensitivity of patients to a Atacurium.

As with other non-depolarising neuromuscular blockers hypophosphataemia may prolong recovery. Recovery may be hastened by correcting this condition.

Atacurium should be administered over a period of 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, for example those who are hypovolaemic.

Atacurium is inactivated by high pH and so must not be mixed in the same syringe with thiopental or any alkaline agent.
When a small vein is selected as the injection site, Atacurium should be flushed through the vein with physiological saline after injection. When other anaesthetic drugs are administered through the same in-dwelling needle or cannula as Atacurium it is important that each drug is flushed through with an adequate volume of physiological saline. Atracurium besilate is hypotonic and must not be administered into the infusion line of a blood transfusion.
Studies in malignant hyperthermia in susceptible animals (swine), and clinical studies in patients susceptible to malignant hypothermia indicate that Atacurium does not trigger this syndrome.
In common with other non-depolarising neuromuscular blocking agents, resistance may develop in patients suffering from burns. Such patients may require increased doses, dependent on the time elapsed since the burn injury and theextent of the burn.
Intensive Care Unit (ICU) patients: When administered to laboratory animals in high doses, Laudanosine, a metabolite of a Atacurium has been associated with transient hypotension and, in some species, cerebral excitatory effects. Although seizures have been seen in ICU patients receiving atracurium, a causal relationship to laudanosine has not been established (see Undesirable Effects).

4.5 Interaction with other drugs, other forms of interactions:
The neuromuscular block produced by Atacurium may be increased by the concomitant use of inhalational anaestheticssuch as halothane, isoflurane and enflurane.
In common with all non-depolarising neuromuscular blocking agents the magnitude and/or duration of a non-depolarisingneuromuscular block may be increased as a result of interaction with:

- antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin
- anti-arrhythmic drugs: propranolol, calcium channel blockers, lidocaine, procainamide and quinidine
- diuretics: furosemide and possibly mannitol, thiazide diuretics and acetazolamide
- magnesium sulfate
- ketamine
- lithium salts and quinine.
- ganglion blocking agents, trimetaphan, hexamethonium.

Rarely certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to Atacurium would be consequent on such a development. Such drugs include various antibiotics, β- blockers (propranolol, oxprenolol), antiarrhythmic drugs (procainamide, quinidine), antirheumatic drugs (chloroquine, D- penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.
The onset of non-depolarising neuromuscular block is likely to be lengthened and the duration of block shortened inpatients receiving chronic anticonvulsant therapy.
The administration of combinations of non-depolarising neuromuscular blocking

agents in conjunction with Atacurium may produce a degree of neuromuscular blockage in excess of that which might be expected were an equipotent total dose of Atacurium administered. Any synergistic effect may vary between different drug combinations.

A depolarising muscle relaxant such as suxamethonium chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarising blocking agents such as atracurium, as this may result in a prolongedand complex block which can be difficult to reverse with anticholinesterase drugs.

Treatment with anticholinesterases, commonly used in the treatment of Alzheimer's disease e.g. donepezil, may shorten the duration and diminish the magnitude of neuromuscular blockade with atracurium.

4.6 Fertility, Pregnancy & Lactation:

Pregnancy

Atracurium crosses the placenta but there have been no demonstrated adverse effects in the foetus or newborn infant. Animal studies have indicated that atracurium has no adverse effects on foetal development. As with all neuromuscular blocking agents, the use of Atracurium Besilate solution for injection/infusion in the first three months of pregnancy should be avoided and it should not be used during the second and third trimesters unless clearly necessary.

Atracurium Besilate solution for injection/infusion is suitable for maintenance of muscle relaxation during caesarean section as it does not cross the placenta in clinically significant amounts following recommended doses. In an open-label study, atracurium besilate (0.3 mg/kg) was administered to 26 pregnant women during delivery by caesarean section. No harmful effects were attributable to atracurium in any of the newborn infants, although small amounts of atracurium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following caesarean section during which a neuromuscular blocking agent has been administered.

Anaesthesia during the third trimester of pregnancy exposes the mother to Mendelson syndrome (acid pneumopathy due to gastric acid aspiration). If a muscle relaxant is used at induction of anaesthesia, one should be chosen with a short onset and duration of action and low placental transfer and used in the lowest dose required to induce adequate neuromuscular relaxation. In patients receiving magnesium sulphate, the reversal of neuromuscular blockade may be unsatisfactory and the Atracurium Besilate solution for injection/infusion dose should be lowered as indicated.

Breast-feeding

Atracurium has a relatively high molecular weight and is highly ionized at physiologic pH, both factors that markedly reduce transfer into milk. In

addition, even though milk is slightly more acidic than plasma, any atracurium transferred into milk would be rapidly degraded. Nevertheless, in view of the potential respiratory depressant effect on the neonate, especially if premature, breast-feeding should be discontinued for 24 hours after administration of Atracurium Besilate solution for injection/infusion.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and operate machine:

Atracurium Besilate solution for injection/infusion in combination with other anaesthetic agents can have major influence on the ability to drive and use machines. 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:

The adverse effects are reported in decreasing order of frequency within each system order class (SOC).

As with most neuromuscular blocking agents, the potential exists for undesirable effects suggestive of histamine release in susceptible patients. In clinical trials (875 patients) reports of skin flushing ranged from 1% at doses up to 0.3 mg/kg, to 29% at doses of 0.6 mg/kg or greater. The incidence of transient hypotension ranged from 1% to 14% respectively for the corresponding dosages.

Table for frequency of adverse reactions for Atracurium Besilate solution for injection/infusion

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000**	**Very rare (< 1/10,000)**	**Not known (cannot be estimated from the available data)**
Immune system disorders				Anaphylactic shock,. anaphylactic reaction, anaphylactoid reaction	
Cardiac disorders	Tachycardia, bradycardia		Cardiac arrest, cardiac failure*		
Vascular disorders	Hypertension, hypotension, vasodilatation (flushing)				
Respiratory, thoracic and mediastinal disorders	Wheezing	Bronchospasm	Dyspnoea, laryngospasm	Hypoxemia	Bronchial secretions

Skin and subcutaneous tissue disorders	Localised skin reactions, rash, itching	Generalised erythema, hives	Angioneurotic oedema, urticaria		
General disorders and administration site conditions	Reaction at injection site				
Injury, poisoning and procedural complications					Neuromuscular block prolonged

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose:
Prolonged muscle paralysis and its consequences are the main signs of overdose. There is limited experience with atracurium overdosage following parenteral administration. The possibility of iatrogenic overdosage can be minimised by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Atracurium Besilate solution for injection/infusion are likely to produce symptoms consistent with extensions of the usual pharmacological effects. Overdosage may increase the risk of histamine release and adverse cardiovascular effects, especially hypotension. If cardiovascular support is necessary, this should include proper positioning, fluid administration, and the use of vasopressor agents if necessary. It is essential to maintain a patent airway with assisted positive pressure ventilation until spontaneous respiration is adequate. Full sedation will be required since consciousness is not impaired. The duration of neuromuscular blockade may be prolonged, and a peripheral nerve stimulator should be used to monitor recovery. Recovery may be hastened by the administration of an anticholinesterase agent such as neostigmine or pyridostigmine in conjunction with an anticholinergic agent such as atropine, once evidence of spontaneous recovery is present.

5 Pharmacological Properties:
5.1 Pharmacodynamic Properties:
Pharmacotherapeutic group: Peripherally acting muscle relaxants: Other quaternary ammonium compounds.ATC code: M03AC04.
Atracurium is a highly selective competitive (non-depolarising) neuromuscular blocking agent with an intermediate duration of action. Non-depolarising agents antagonise the neurotransmitter action of acetylcholine by binding with receptor sites on the motor-end-plate. Atracurium can be used in a wide range of surgical procedures and to facilitatecontrolled ventilation.
Paediatric population:
The limited data in neonates from literature reports suggest variability in the

time to onset and duration of action ofatracurium in this population as compared to children.

5.2 Pharmacokinetic Properties:

The pharmacokinetics of Atracurium in man are essentially linear with the 0.3-0.6 mg/kg dose range. The elimination half-life is approximately 20 minutes, and the volume of distribution is 0.16 L/kg. Atracurium is 82% bound to plasma proteins.

Atracurium is degraded spontaneously mainly by a non-enzymatic decomposition process (Hofmann elimination) which occurs at plasma pH and at body temperature and produces breakdown products which are inactive. Degradation also occurs by ester hydrolysis catalysed by non-specific esterases. Elimination of atracurium is not dependent on kidney orliver function.

The main breakdown products are laudanosine and a monoquaternary alcohol which have no neuromuscular blocking activity. The monoquaternary alcohol is degraded spontaneously by hofmann elimination and excreted by the kidney. Laudanosine is excreted by the kidney and metabolised by the liver. The half-life of laudanosine ranges from 3-6h in patients with normal kidney and liver function. It is about 15h in renal failure and is about 40h in renal and hepatic failure. Peak plasma levels of laudanosine are highest in patients without kidney or liver function and average 4 µg/ml with wide variation.

Concentration of metabolites are higher in ICU patients with abnormal renal and/or hepatic function (see Special Warnings and Special Precautions for Use). These metabolites do not contribute to neuromuscular block.

5.3 Preclinical Safety Data :

Animal Toxicology and/or Pharmacology

Carcinogenicity: Carcinogenicity studies have not been performed.

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 Pharmaceutical Particulars:

6.1 List of Excipients:

Benzene Sulphonic Acid IH Water for Injection USP

6.2 Incompatibilities:

None

6.3 Shelf life: 24 Months

6.4 Special precautions for storage: As per USP, Preserve in single dose container, Type- I Glass in a refrigerator and protect from freezing. Protect from light.

6.5 Nature and contents of container:

ATACURIUM (Atracurium Besylate Injection USP 10mg/ml) is filled in 3 ml USP Type-I clear glass snap off ampoule with red ring. 5 such ampoules are packed in a blister. 1 such blister packed in a carton with pack insert.

ATACURIUM (Atracurium Besylate Injection USP 10 mg/ml) is filled in a 5 ml

USP
Type-I clear glass snap off ampoule with red ring. 5 Such ampoules are packed in a blister. 1 Such blister is packed in a carton with pack insert.

6.6 Special precaution for disposal : Not Applicable

7 Marketing Authorisation Holder:

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8 Marketing Authorisation Number

H2025/CTD11839/22874

9 Date of Registration /renewal of the Authorisation:

9th July 2025

10 Date of revision of the text:

9th July 2025