SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atracurium besilate 10mg/ml Solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 10 mg of atracurium besilate.

One ampoule with 2.5 ml solution contains 25 mg atracurium besilate.
One ampoule with 5 ml solution contains 50 mg atracurium besilate.
One vial with 25 ml solution contains 250 mg atracurium besilate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atracurium besilate is a highly selective, competitive or non-depolarising neuromuscular blocking agent. It is used as an adjunct to general anaesthesia or sedation in the intensive care unit (ICU), to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation.

4.2 Posology and method of administration

Route of administration: Intravenous injection or continuous infusion.

Used by injection in adults: atracurium besilate is administered by intravenous injection.
The dosage range recommended for adults is 0.3 to 0.6 mg/kg (depending on the duration of full block required) and will provide adequate relaxation for about 15 to 35 minutes.

Endotracheal intubation can usually be accomplished within 90 seconds from the intravenous injection of 0.5 to 0.6 mg/kg.

Full block can be prolonged with supplementary doses of 0.1 to 0.2 mg/kg as required. Successive supplementary dosing does not give rise to accumulation of neuromuscular blocking effect.

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.

The neuromuscular block produced by atracurium besilate can be rapidly reversed by standard doses of anticholinesterase agents, such as neostigmine and edrophonium, accompanied or preceded by atropine, with no evidence of recurarisation.

Use as an infusion in adults: After an initial bolus dose of 0.3 to 0.6 mg/kg, atracurium besilate can be used to maintain neuromuscular block during long surgical procedures by administration as a continuous infusion at rates of 0.3 to 0.6mg/kg/hour.

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

Atracurium besilate is compatible with the following infusion solutions for the times stated below:

Infusion solution	*Period of stability*
Sodium Chloride Intravenous Infusion British Pharmacopoeia (BP) (0.9% w/v)	24 hours
Glucose Intravenous Infusion BP (5% w/v)	8 hours
Ringer's Injection United States Pharmacopoeia (USP)	8 hours
Sodium Chloride (0.18%w/v) and Glucose (4% w/v) Intravenous Infusion BP	8 hours
Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution for Injection)	4 hours

When diluted in these solutions to give atracurium besilate concentrations of 0.5 mg/ml and above, the resultant solutions will be stable in daylight for the stated periods at temperatures of up to 30°C.

Use in Children: The dosage in children over the age of one month is similar to that in adults on a bodyweight basis.

Use in Neonates: The use of atracurium besilate is not recommended in neonates since there are insufficient data available (see section 5.1).

Use in the elderly: atracurium besilate may be used at standard dosage in elderly patients. It is recommended, however, that the initial dose be at the lower end of the range and that it be administered slowly.

Use in patients with reduced renal and/or hepatic function: atracurium besilate may be used at standard dosage at all levels of renal or hepatic function, including end stage failure.

Use in patients with cardiovascular disease: In patients with clinically significant cardiovascular disease, the initial dose of atracurium besilate should be administered over a period of 60 seconds.

Use in intensive care unit (ICU) patients: After an optional initial bolus dose of atracurium besilate of 0.3 to 0.6 mg/kg, atracurium besilate can be used to maintain neuromuscular block by administering a continuous infusion at rates of between 11 and 13 micrograms/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 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.

Monitoring: In common with all neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of atracurium besilate in order to individualise dosage requirements.

4.3 Contraindications

Atracurium is contraindicated in patients known to be hypersensitive to atracurium, cisatracurium or benzenesulfonic acid (see section 4.4, Special Warnings and Precautions for Use).

4.4 Special warnings and precautions for use

Precautions: **In common with all the other neuromuscular blocking agents, atracurium besilate paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness. Atracurium besilate 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 atracurium besilate administration. Caution should be exercised in administering atracurium besilate 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 other neuromuscular blockers.

Monitoring of serial creatinine phosphate (cpk) values should be considered in asthmatic patients receiving high dose corticosteroids and neuromuscular blocking agents in ICU.

Atracurium besilate does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, atracurium besilate 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 or decrease the sensitivity of patients to atracrium.

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

Atracurium besilate 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.

Atracurium besilate 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, atracurium besilate 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 atracurium besilate 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 atracurium besilate 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 the extent of the burn.

Intensive Care Unit (ICU) patients: When administered to laboratory animals in high doses, Laudanosine, a metabolite of atracrium 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 medicinal products and other forms of interaction

The neuromuscular block produced by atracurium besilate may be increased by the concomitant use of inhalational anaesthetics such as halothane, isoflurane and enflurane.

In common with all non-depolarising neuromuscular blocking agents the magnitude and/or duration of a non-depolarising neuromuscular 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
- ganglion blocking agents, trimetaphan, hexamethonium.

Rarely certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to atracurium besilate 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 in patients receiving chronic anticonvulsant therapy.

The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with atracurium besilate may produce a degree of neuromuscular blockage in excess of that which might be expected were an equipotent total dose of atracurium besilate 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 prolonged and 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 and lactation

Fertility
Fertility studies have not been performed

Pregnancy
Animal studies have indicated that atracurium besilate has no significant effects on foetal development.

In common with all neuromuscular blocking agents, atracurium besilate should be used during pregnancy only if the potential benefit to the mother outweighs any potential risk to the foetus.

Atracurium besilate is suitable for maintenance of muscle relaxation during Caesarean section as it does not cross the placenta in clinically significant amounts following recommended doses.

Breast-feeding
It is not known whether atracurium besilate is excreted in human milk.

4.7 Effects on ability to drive and use machines

This precaution is not relevant to the use of atracurium. Atracurium will always be used in combination with a general anaesthetic and therefore the usual precautions relating to performance of tasks following general anaesthesia apply.

4.8 Undesirable effects

The most commonly reported adverse reactions during treatment are hypotension (mild, transient) and skin flushing, these events are attributed to histamine release. Very rarely, severe anaphylactoid or anaphylactic reactions have been reported in patients receiving atracurium in conjunction with one or more anaesthetic agents.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common > 1/10, common >1/100 and < 1/10, uncommon >1/1000 and < 1/100, rare >1/10,000 and < 1/1000, very rare < 1/10,000.

Very common, common and uncommon frequencies were determined from clinical trial data. Rare and very rare frequencies were generally derived from spontaneous data. The frequency classification "Not known" has been applied to those reactions where a frequency could not be estimated from the available data.

Clinical Trial Data

Vascular Disorders

Common	Hypotension (mild, transient)#, Skin flushing#

Respiratory, thoracic and mediastinal disorders

Uncommon	Bronchospasm#

Post-Marketing Data

Immune system disorders

Very rare	Anaphylactic reaction, anaphylactoid reaction including anaphylactic shock, circulatory failure and cardiac arrest

Very rarely, severe anaphylactoid or anaphylactic reactions have been reported in patients receiving atracurium in conjunction with one or more anaesthetic agents.

Nervous system disorder

Not known Seizures

There have been reports of seizures in ICU patients who have been receiving atracurium concurrently with several other agents. These patients usually had one or more medical conditions predisposing to seizures (e.g. cranial trauma, cerebral oedema, viral encephalitis, hypoxic encephalopathy, uraemia). A causal relationship to laudanosine has not been established. In clinical trials, there appears to be no correlation between plasma laudanosine concentration and the occurrence of seizures.

Skin and subcutaneous tissue disorders

Rare Urticaria

Musculoskeletal and connective tissue disorders

Not known Myopathy, muscle weakness

There have been some reports of muscle weakness and/or myopathy following prolonged use of muscle relaxants in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids. These events have been seen infrequently in association with atracurium and a causal relationship has not been established.

Events which have been attributed to histamine release are indicated by a hash (#)

Description of selected adverse reactions

Anaphylactic reaction, anaphylactoid reaction including anaphylactic shock: Very rarely, severe anaphylactoid or anaphylactic reactions including anaphylactic shock have been reported in patients receiving atracurium in conjunction with one or more anaesthetic agents.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Symptoms: Prolonged muscle paralysis and its consequences are the main signs of overdosage.

Management: It is essential to maintain a patient airway together with assisted positive pressure ventilation until spontaneous respiration is adequate. Full sedation will be required since consciousness is not impaired. Recovery may be hastened by the administration of anticholinesterase agents accompanied by atropine or glycopyrrolate, 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 facilitate controlled ventilation.

Paediatric population:
The limited data in neonates from literature reports suggest variability in the time to onset and duration of action of atracurium in this population as compared to children (see section 4.2).

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 or liver 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

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 Sulfonic acid
Water for Injections

6.2 Incompatibilities

None.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at temperatures between 2 and 8^{o}C. Do not freeze. Keep container in the outer carton in order to protect from light.

Any unused atracurium besilate from opened ampoules or vials should be discarded.

6.5 Nature and contents of container

Neutral glass ampoules or vials. Vials are closed with a rubber stopper, sealed with an aluminium collar and fitted with a plastic flip-off top. Pack sizes: Boxes of 5 x 2.5 ml ampoules, 5 x 5 ml ampoules and 2 x 25 ml vials.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
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City West Business Campus,
Dublin 24, Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 39699/0091

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