SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atracurium 10mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml 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 ampoule with 25 ml solution contains 250 mg atracurium besilate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection and Concentrate for solution for infusion
Clear and colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atracurium is used intravenously as an adjunct to general anaesthesia, during surgical and other procedures and in intensive care to facilitate tracheal intubation and controlled ventilation.

4.2 Posology and method of administration

Route of administration:
Intravenous injection or continuous infusion.

Posology

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

Use in anaesthesia

- In adults: Use as an injection

Atracurium besilate is administered by intravenous injection and must not be applied intramuscularly.

Relaxation
The dosage range recommended for adults is 0.3 to 0.6 mg atracurium/kg (depending on the duration of full block required). This dose will provide adequate relaxation for about 15 to 35 minutes.

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

Repeated dose
Full block can be prolonged with supplementary doses of 0.1 to 0.2 mg atracurium/kg. Generally, the first maintenance dose is required 20 to 45 minutes after the initial bolus dose, then typically at 15 to 25 minutes intervals, however, the need for maintenance doses should be determined by the individual patient's requirements and responses. Successive supplementary dosing does not produce accumulation in neuromuscular blocking effect.

As measured by the restoration of the tetanic response to 95% of normal neuromuscular function, spontaneous recovery occurs about 35 minutes after a full block.

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 or glycopyrrolate, with no evidence of recurarisation.

- In adults: Use as an infusion

Atracurium besilate is hypotonic and must not be administered via the infusion system of a blood transfusion. In this case atracurium besilate has to be administered via a separate infusion line.

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

Atracurium besilate can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates.

Induced hypothermia with body temperature of 25 to 26°C reduces the rate of degradation of atracurium besilate, therefore full neuromuscular block may be maintained with approximately half the original infusion rate at these low temperatures.

- Use in paediatric population

On a bodyweight basis the dosage in children over the age of 1 month is similar to that in adults.

Use in neonates:
The use of atracurium is not recommended in neonates since there are insufficient data available (see section 5.1). In case of a necessary neuromuscular blockade also in newborn or premature newborn the dose has to be significantly lowered.

- Use in special populations

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 endstage 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 patients suffering from burns:
As 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.

Use in patients in intensive care units (ICU):

When there is a need of atracurium besilate for long-term mechanical ventilation in intensive care units, the benefit to risk ratio of neuromuscular block must be considered. After an initial bolus dose of 0.3 - 0.6 mg/kg, Atracurium besilate can be used to maintain neuromuscular block by administration of a continuous infusion of between 11 and 13 micrograms/kg/min (0.65 - 0.78 mg/kg/h). There is, however, a great variety of dosage requirements between patients. Patients may require infusion rates of as low as 4.5

micrograms/kg/min (0.27 mg/kg/h) or as high as 29.5 micrograms/kg/min (1.77 mg/kg/h). Dosage requirements may change over time.
The speed of spontaneous recovery from neuromuscular block after infusion of atracurium besilate in ICU patients is independent of the duration of administration. Spontaneous recovery can be expected of a train-of-four ratio of more than 0.75 (the ratio of the peak of the fourth to the first contraction in a train of four) which occurs on average in approximately 60 minutes with a range of approximately 32 - 108 minutes (n = 6) has been observed in clinical trials.
The few findings currently available regarding long-term use of atracurium besilate indicate only minor influence of haemofiltration and haemodialysis on the plasma levels of atracurium besilate and its metabolites.
The effect of the haemoperfusion on the level of Atracurium and its metabolites in plasma is not known.

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.

4.4 Special warnings and precautions for use

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 has to be administered only with adequate general anaesthesia and only by or under the close supervision of an experienced anaesthetist, with adequate facilities and staff for endotracheal intubation and artificial ventilation, as well as an antidote, immediately at hand.

Atracurium besilate must not be applied intramuscularly.

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 atracurium.

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

As with other neuromuscular blocking agents, 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 cpk (Creatinphosphokinase) should be considered in asthmatic patients receiving high-dose corticosteroids and neuromuscular blocking agents in ICU.

Histamine release can be minimized by slow administration or by divided doses over at least one minute.

Atracurium besilate is hypotonic and must not be administered via the infusion system of a blood transfusion, because it might cause haemolysis. Note the pH: 3.2 to 3.7. (For incompatibility see section 6.2)

Atracurium is inactivated by high pH and so must not be mixed in the same syringe with thiopentone or any alkaline agent.

Atracurium besilate should be administered - slowly or in partial doses - over a period of 60 - 120 seconds to patients abnormally susceptible to falls in arterial blood pressure, for example those who are hypovolaemic.

Atracurium besilate does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, atracurium besilate has no significant effects on heart rate in the recommended dosage range. Bradycardia produced by other anaesthetic agents or by vagal stimulation during surgery will not be counteracted by atracurium besilate and may therefore occur at a higher severity.

After injecting atracurium besilate into a small vein, physiological saline solution should be flushed through the vein. If other anaesthetic medicinal products are administered through the same in-dwelling needle or cannula as atracurium besilate, it is important that after each medicinal product an adequate volume of water for injection or physiological saline is flushed through.

In common with other non-depolarising neuromuscular blocking agents, resistance may develop in patients suffering from burns (see section 4.2). Such patients may require increased doses dependent on the time elapsed since the burn injury and the extent of the burn.

Atracurium besilate has no direct effect on the intra-ocular pressure, which makes it suitable for use in ophthalmic surgery.

Studies in malignant hyperthermia in susceptible animals (swine) and clinical studies in patients susceptible to malignant hyperthermia indicate that atracurium besilate does not trigger this syndrome.

Intensive Care unit (ICU) Patients: When administered to laboratory animals in high doses, laudanosine, a metabolite of atracurium, 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 section 4.8).

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 enflurane, sevofluran and desflurane.

As 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, clindamycin and vancomycin;
- antiarrhythmic medicinal products: lidocaine, procainamide and quinidine;
- beta-blocking agents: propranolol;
- calcium channel blockers;
- diuretics: furosemide and possibly mannitol, thiazide diuretics;
- acetazolamide;
- magnesium sulfate ;
- ketamine;
- lithium salts;
- dantrolene;
- ganglion blocking agents: trimethaphan, hexamethonium.

Seldom, certain medicinal products may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to atracurium besilate would follow.
Such medicinal products include:

- various antibiotics;
- beta-blockers (propranolol, oxprenolol);
- antiarrhythmic medicinal products (procainamide, quinidine);
- antirheumatic drugs (chloroquine, D-penicillamine)
- trimethaphan;
- chlorpromazine;
- steroids;
- phenytoin;
- 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 (phenytoine, carbamazepine).

The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with atracurium besilate may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of atracurium besilate administered. Any synergistic effect may vary between different medicinal product 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 rather difficult to reverse with anticholinesterase medicinal products.

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

There are no adequate data on the use of atracurium besilate during pregnancy. Although animal experiments show no evidence of disturbances in embryonic development, atracurium besilate should only be administered during pregnancy after careful risk-benefit assessment. Placental transfer is low. Applications within the recommended dose range in caesarean section patients showed no detrimental effects on the new-born (see also toxicological properties).Therefore atracurium besilate is also suitable for maintenance of muscle relaxation during caesarean section.

Lactation

It is not known whether atracurium besilate passes into breast milk. Due to the short half-life, an influence on the infant is not to be expected if the mother starts breast-feeding (again) after the effects of the substance have worn off. As precaution restart breast-feeding 24 hours after administration of atracurium besilate.

4.7 Effects on ability to drive and use machines

As the medicinal product is administered under general anaesthesia, the patient must not drive, operate machinery or work in exposed situations after anaesthesia. The time factor should be decided individually by the physician.

The patient should be accompanied on his way home and should not ingest alcohol.

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 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
Very rare: Anaphylactic and anaphylactoid reactions including shock, circulatory failure and cardiac arrest.
Very rarely, severe anaphylactoid or anaphylactic reactions have been reported in patients receiving atracurium besilate in conjunction with one or more anaesthetic agents.

Nervous system disorders
Very rare: Seizures

There have been reports of seizures in patients in ICUs who had been receiving atracurium besilate simultaneously with other pharmacological agents. These patients generally had one or more medical conditions which made them susceptible to seizures (such as brain injury, cerebral oedema, viral encephalitis, hypoxic encephalopathy, uraemia). A causal relationship to laudanosine (a metabolite of atracurium besilate) has not been established. Even after weeks of continuous infusion, there appear to be no correlation between plasma laudanosine concentration and occurrence of seizures in clinical trials (see also section 5.2).

Cardiac disorders
Common: Tachycardia

Vascular disorders
Common: Mild transient hypotension, skin flushing

Respiratory, thoracic and mediastinal disorders
Common: Wheezing, bronchospasm
Very rare: Laryngospasm

Skin and subcutaneous tissue disorders
Common: Urticaria

Musculoskeletal and connective tissue disorders
Very rare: Myopathy, muscle weakness.

After prolonged use of atracurium besilate in severely ill ICU patients myasthenia and/or myopathy have been observed. The majority of these patients received concomitant corticosteroids. Causal connection with atracurium besilate therapy is not established.

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 and signs:
The main signs of overdose are prolonged muscle paralysis and its consequences.

Treatment:
If cardiovascular support is necessary, this should include proper positioning of the patient, fluid administration/volume substitution, and the use of vasopressor agents if necessary.

It is essential to maintain a patent airway together with assisted positive pressure ventilation until adequate spontaneous respiration reappears.

Full sedation will be required since consciousness is not impaired.

Recovery may be accelerated 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

Pharmaco-therapeutic group: Muscle relaxants, peripherally acting; other quarternary ammonium compounds.

ATC code: M03A C04.

Atracurium besilate is a non-depolarising muscle relaxant with medium duration of action.

The active ingredient, atracurium besilate, interacts specifically with neurophysiological processes at the motor end-plate by competitively displacing acetylcholine from its receptor sites.

As a result of end-plate occupation by atracurium besilate, further depolarisation is inhibited. Subsequently, skeletal muscles are paralysed since stimulation by motoric nerves cannot be transmitted to the muscles.

Through inhibition of acetylcholine degradation by means of cholinesterase inhibitors, e.g. neostigmine or edrophonium, an increase of acetylcholine concentration is achieved at all cholinergic synapses. The balance between atracurium besilate (antagonist) and acetylcholin (agonist) is shifted in favour of the latter. As a result, stimulation of the muscle can reoccur.

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.

When given to laboratory animals, cerebral excitatory effects have been associated with a metabolite of atracurium, laudanosine. Although seizures have been observed in patients in ICUs who were receiving atracurium, they were not attributed in any case to laudanosine or to atracurium, even after weeks of continuous infusion.

5.3 Preclinical safety data

Mutagenicity

Atracurium besilate was not mutagenic in bacteria and in myeloid cells of rats. *In vitro*, minor mutagenic activity in mammalian cells was observed only in cytotoxic concentrations.

Carcinogenicity:
Carcinogenicity studies have not been performed.

Embryotoxicity/ Fetotoxicity:
From the results of animal experiments it appears that atracurium besilate has no significant effect on embryonic development. Studies of the effects on the foetal development phase were not carried out.

Fertility:
Fertility studies were not carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection
Benzenesulfonic acid

6.2 Incompatibilities

Atracurium besilate is inactivated by high pH and so must not be mixed in the same syringe with thiopentone or any alkaline agent.
Therefore the cannula has to be flushed between infusion of atracurium besilate and thiopentone in order to avoid the formation of aggregates, which might cause an anaphylactoid reaction.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

Shelf life after opening
The solution has to be used immediately after opening the ampoule.

Shelf life after dilution
For shelf life after dilution, see section 6.4.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Keep the ampoules in the outer carton.
Do not freeze.

When diluted in compatible solutions (see section 6.6) 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. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Box of 1 ampoule with 2.5 ml (Type I colourless glass)
Box of 5 ampoules with 2.5 ml (Type I colourless glass)
Box of 10 ampoules with 2.5 ml (Type I colourless glass)
Box of 5x5 ampoules with 2.5 ml (Type I colourless glass)
Box of 5x10 ampoules with 2.5 ml (Type I colourless glass)
Box of 1 ampoule with 5 ml (Type I colourless glass)
Box of 5 ampoules with 5 ml (Type I colourless glass)
Box of 10 ampoules with 5 ml (Type I colourless glass)
Box of 5x5 ampoules with 5 ml (Type I colourless glass)
Box of 5x10 ampoules with 5 ml (Type I colourless glass)
Box of 1 ampoule with 25 ml (Type I colourless glass)
Box of 2 ampoules with 25 ml (Type I colourless glass)
Box of 5 ampoules with 25 ml (Type I colourless glass)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Atracurium besilate is compatible with the following infusion solutions:

Infusion Solution	*Period of Stability*
1. Sodium Chloride Intravenous Infusion BP (0.9% w/v)	24 hours
2. Glucose Intravenous Infusion BP (5% w/v)	8 hours
3. Ringer's Injection USP	8 hours
4. Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion BP	8 hours
5. Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution for Injection)	4 hours

Store all medical products properly and keep them out of reach of children.

Prior to administration it is recommended to inspect the product visually and discard any product where the usual appearance of the product has changed or if the container is damaged.

Only clear solutions practically free from particles should be used.

The product is for single use only.

Any unused solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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