SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atracurium besilate 10 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 10 mg atracurium besilate.

One ampoule with 2.5 ml solution contains 25 mg atracurium besilate.

One ampoule with 5.0 ml solution contains 50 mg atracurium besilate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion

The product is a clear and colourless solution with a pH of 3.00 – 3.65 and an osmolality of 10 - 30 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous use during surgical and other procedures and in intensive care.

Atracurium besilate is used as an adjunct to general anaesthesia, to facilitate tracheal intubation and controlled ventilation.

4.2 Posology and method of administration

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

- *Use as an injection in adults*

Atracurium besilate 10 mg/ml solution for injection/infusion is administered by intravenous injection and must not be administered intramuscularly.

Relaxation

The dosage range recommended for adults is 0.3 to 0.6 mg atracurium besilate/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 besilate /kg.

Repeated dose

Full block can be prolonged with supplementary doses of 0.1 to 0.2 mg atracurium besilate /kg. Generally, the first maintenance dose is required 20 to 45 minutes after the initial bolus injection, then typically at 15 to 25 minute 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.

Once evidence of spontaneous recovery is present, 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.

- *Use as an infusion in adults*

Atracurium besilate 10 mg/ml 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.

Atracurium besilate 10 mg/ml can be diluted with the infusion solutions listed in section 6.6.

- *Use in children, in the elderly, in patients with reduced renal and/or hepatic function, in patients with cardiovascular disease, in patients suffering from burns and in patients in intensive care units (ICU)*

Use in children:

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

Use in Neonates:

The use of atracurium besilate 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 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:

Patients with severe cardiovascular diseases may react more sensitively to transient states of hypotony (see also section 4.4). In these patients, atracurium besilate should therefore be administered slowly and/or in divided doses over 1 - 2 minutes.

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 optional 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 (0.66 - 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. Therefore, the rate of infusion should be adjusted by peripheral nerve monitoring.

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 32 - 108 minutes (n = 6) 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 besilate and its metabolites in plasma is not known.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

As with all 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 or with adequate sedation in ICU patients and only by an experienced anaesthetist, with adequate facilities and staff for endotracheal intubation and artificial ventilation, and with an antidote, immediately available.

Atracurium besilate 10 mg/ml must not be administered intramuscularly.

As with other non-depolarising neuromuscular blocking agents, increased sensitivity to atracurium besilate may be expected in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of non-depolarising neuromuscular blocking agents has been noted. A reduced dosage of atracurium besilate and the use of a peripheral nerve stimulator for assessing neuromuscular blockade is especially important in these patients. Similar precautions should be taken in patients with severe acid-base and/or electrolyte imbalance or carcinomatosis.

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.

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

Especially in patients with a history of allergy or asthma, individual cases of bronchospasm have to be considered. In such cases, use of atracurium besilate has to be carefully monitored. Monitoring of creatine phosphokinase should be considered in asthmatic patients receiving high-dose corticosteroids and neuromuscular blocking agents in ICU.

Atracurium besilate 10 mg/ml 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.

After injecting atracurium besilate 10 mg/ml 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 injections or physiological saline is flushed through.

Atracurium besilate does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, atracurium besilate has no clinically relevant 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 with greater severity.

Atracurium besilate 10 mg/ml is hypotonic and must not be administered via the infusion system of a blood transfusion, because it might cause haemolysis. Note the pH: 3.0 to 3.7 (for incompatibility see also section 6.2).

In common with other non-depolarising neuromuscular blocking agents, resistance may develop in patients suffering from burns (see also section 4.2).

Notes:

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.

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, sevoflurane 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 sulphate;
- 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);
- 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 (phenytoin, 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 besilate, as this may result in a prolonged and complex block which can be difficult to reverse with anticholinesterase medicinal products.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data on the use of atracurium besilate during pregnancy. Animal studies of effects on pregnancy, embryo/foetal development, parturition and post natal development are incomplete (see section 5.3). 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. Therefore, atracurium besilate is also suitable for maintenance of muscle relaxation during caesarean section.

Breastfeeding

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 a 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

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)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders

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

Nervous system disorders

Very rare: 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). Even after weeks of continuous infusion, there appears to be no correlation between plasma laudanosine concentration and appearance of seizures in clinical trials (see also section 5.2).

Cardiac disorders

Common: Tachycardia

Vascular disorders

Common: Mild transient hypotension

Respiratory, thoracic and mediastinal disorders

Common: Bronchospasm, wheezing

Very rare: Laryngospasm

Skin and subcutaneous tissue disorders

Common: Urticaria, skin flushing

Musculoskeletal and connective tissue disorders

Very rare: 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 at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Signs:

The main signs of over-dose 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

Pharmacotherapeutic group: muscle relaxants, peripherally acting agents; Other quaternary ammonium components

ATC code: M03A C04.

Atracurium besilate 10 mg/ml is a non-depolarising muscle relaxant with medium duration of action.

The active substance, 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 motor 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 acetylcholine (agonist) is shifted in favour of the latter. As a result, stimulation of the muscle can reoccur.

Paediatric population:

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

5.2 Pharmacokinetic properties

The onset and duration of effect of atracurium besilate are dose-dependent.

In man, following the administration of 0.3 mg atracurium besilate/kg, plasma concentrations of 3 micrograms/ml were measured after 3 minutes.

Atracurium besilate is inactivated by:

1. Hofmann elimination, a non-enzymatic process which occurs at physiological pH and temperature,

2. Ester hydrolysis catalysed by non-specific esterases.

Variations in the blood pH and body temperature in patients within the physiological range will not significantly alter the duration of action of atracurium besilate.

Tests with plasma from patients with low levels of pseudocholinesterase show that the inactivation of atracurium besilate proceeds unaffected.

Plasma protein binding

The plasma protein binding of atracurium besilate is about 82%. Plasma proteins neither influence the rate nor the mode of atracurium besilate catabolism.

Elimination

Elimination half-life for atracurium besilate is 20 to 30 minutes. As the termination of the neuromuscular blocking action of atracurium besilate is not dependent on its hepatic or renal metabolism or excretion, its duration of action, therefore, is unlikely to be affected by impaired renal, hepatic or circulatory function.

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

The metabolites are present at higher concentrations in intensive care patients with limited renal and/or hepatic function. However, these metabolites have no effect on the muscle relaxant action.

5.3 Preclinical safety data

Genotoxicity:

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/ Foetotoxicity:

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 injections

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

Unopened ampoules: 2 years
Opened ampoules:
The product should be used immediately after opening the ampoule.
Prepared infusion solutions:
Chemical and physical in-use stability has been demonstrated in Sodium Chloride Intravenous Infusion BP for up to 24 hours at 30°C and in other common infusion fluids for up to 4 or 8 hours, respectively (see section 6.6).

Solution for Infusion	*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

When diluted in these solutions to administer 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°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep the ampoules in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml or 5 ml ampoules, made of colourless glass, type I.

Box of 5 ampoules with 2.5 ml

Box of 10 ampoules with 2.5 ml

Box of 5 x 10 ampoules with 2.5 ml

Box of 5 ampoules with 5 ml

Box of 10 ampoules with 5 ml

Box of 5 x 10 ampoules with 5 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Atracurium besilate 10 mg/ml can be used for intravenous injection or infusion.

The product should be inspected visually prior to administration (also after dilution). If it is not clear, colourless and free of particles or if the container is damaged the product should be discarded.

For single dose use only.

Any unused solution from opened ampoules should be discarded.

Atracurium besilate 10 mg/ml is compatible with the following solutions for infusion:Sodium Chloride Intravenous Infusion BP (0.9% w/v)

Glucose Intravenous Infusion BP (5% w/v)

Ringer's Injection USP

Sodium Chloride (0.18% w/v) and

Glucose (4% w/v) Intravenous Infusion BP

Compound Sodium Lactate Intravenous Infusion BP

(Hartmann's Solution for Injection)

7 MARKETING AUTHORISATION HOLDER

hameln pharma ltd

Nexus, Gloucester Business Park

Gloucester, GL3 4AG

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 01502/0136

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20/11/2002

Renewal of authorisation: 15/06/2009

10 DATE OF REVISION OF THE TEXT

16/12/2022