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 of solution contains 10 mg of atracurium besilate.
Each ampoule (2.5 ml) contains 25 mg of atracurium besilate.
Each ampoule (5 ml) contains 50 mg of atracurium besilate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear colourless or yellowish solution, free from visible particles.
pH of solution is 3.30 to 3.65 and osmolality is 10 – 30 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicine is used as an adjunct to general anaesthesia to facilitate tracheal intubation, to relax skeletal muscles during surgery or controlled ventilation, and to facilitate mechanical ventilation of patients in the intensive care unit.

4.2 Posology and method of administration

Posology

Adults

Dosage by intravenous injection
Atracurium besilate is administered by intravenous injection. The usual dose for adults ranges from 0.3 to 0.6 mg/kg of body weight (depending on the required duration of full block) and provides adequate relaxation for 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.

Caesarean Section:
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 (0.3-0.6 mg/kg).

Spontaneous recovery of normal muscle tone occurs after approximately 35 minutes when neuromuscular function restored to 95 % of its baseline (measured by the restoration of the tetanic response).

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

Dosage by intravenous infusion
After an initial bolus dose of 0.3 to 0.6 mg/kg, continuous intravenous infusion of atracurium besilate at rates of 0.3 to 0.6 mg/kg/hour can be used during long surgical procedures to maintain adequate neuromuscular block.
Atracurium besilate can be administered by intravenous infusion during cardiopulmonary bypass surgery at the recommended infusion rates.
Induced hypothermia with body temperature of 25 to 26 °C reduces the rate of inactivation of atracurium besilate therefore full neuromuscular block may be maintained with approximately half of the original infusion rate.

Paediatric population
The dosage based on body weight in children over the age 1 month is the same as in adults.
Since there are insufficient data available it is not recommended to administer atracurium besilate to neonates (see section 5.1).

Elderly
The standard dose is administered to elderly patients. It is recommended, however, that the initial dose should be at the lower end of the range and that it should be administered slowly.

Renal or hepatic impairment
No dose adjustment is required in these patients, the standard dose is administered, even in the terminal stages of the disease.

Cardiovascular disease
In patients with clinically significant cardiovascular disease, the initial dose should be administered slowly over a period of 60 seconds.

Intensive care unit(ICU)
After an optional initial bolus dose of atracurium besilate of 0.3 to 0.6 mg/kg the adequate neuromuscular block is maintained by administering of continuous infusion at rate of 11 to 13 microgram/kg/min (0.65-0.78 mg/kg/hour). However, between the individual patients there may be significant differences in the required dose. Dosage requirements may change over time. Some patients may require infusion rates as low as 4.5 microgram/kg/min (0.27 mg/kg/hour) or as high as 29.5 microgram/kg/min (1.77 mg/kg/hour).

Spontaneous recovery of the normal muscular tone in ICU patients is independent on the duration of administration. Spontaneous recovery can be expected of a train-of-four ratio >0.75 (the ratio of the peak of the fourth to the first contraction in a train of four) which occurs on average 60 minutes with a range of 32 to 108 minutes.

Monitoring
As with all neuromuscular blocking agents, regular monitoring of neuromuscular transmission is necessary during administration of atracurium besilate in order to individualise dosage requirements.

Method of administration

Intravenous injection or infusion.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to atracurium, cisatracurium or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

As with other neuromuscular blocking agents, atracurium besilate paralyses the respiratory muscles as well as other skeletal muscles but it has no effect on consciousness. This medicine should be administered only in a unit with adequate facilities for endotracheal intubation and artificial ventilation, with adequate general anaesthesia and by or under the close supervision of an experienced anaesthetist.

Release of histamine may occur in susceptible patients during administration of atracurium besilate. Caution should be exercised in administering atracurium besilate to patients with a history suggestive of an increased sensitivity to the effects of histamine. Bronchospasm may occur especially in patients with a history of allergy or asthma.

Caution should also be exercised when administering atracurium to patients who have shown hypersensitivity to other neuromuscular blocking agents since a high rate of cross-sensitivity (greater than 50 %) between neuromuscular blocking agents has been reported (see section 4.3).

Atracurium besilate has no significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, this medicine in the recommended dosage range has no clinically significant influence on heart rate and it does not counteract the bradycardia produced by other anaesthetic agents or by vagal stimulation during surgery.

As with other non-depolarising neuromuscular blocking agents, increased sensitivity to atracurium besilate may be expected in patients with myasthenia gravis or with other forms of neuromuscular diseases, and with severe electrolyte imbalances.

Atracurium besilate should be administered over a period of 60 seconds in patients who can be unusually sensitive to falls in arterial blood pressure, e.g. in patients with hypovolaemia.

Atracurium besilate is inactivated by high pH, and so must not be mixed in the same syringe with solutions of thiopental or other alkaline solutions.

If a small vein is selected as the injection site, atracurium besilate should be flushed through the vein with, physiological saline solution after injection. If other medicines are administered through the same in-dwelling needle or cannula as atracurium besilate, it is important that each drug is flushed through with a sufficient volume of physiological saline.
This medicine is a hypotonic solution and must not be administered into the same venous access as a blood transfusion.

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

In common with other non-depolarising neuromuscular blocking agents, resistance to myorelaxative effect of atracurium besilate may develop in patients suffering from burns. Such patients may require higher doses, dependent on the time elapsed since the burn and on the extent of the burn.

Patients in the intensive care unit
Administration of laudanosine, one of metabolites of atracurium besilate, to laboratory animals has been associated with transient hypotension and, in some species, cerebral excitatory effects.
Although seizures have been observed in patients, receiving atracurium besilate in the intensive care unit, 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

Concomitant use of inhalation anaesthetics such as halothane, isoflurane or enflurane may increase the neuromuscular block produced by atracurium besilate.
As with all non-depolarising neuromuscular blocking agents, non-depolarising neuromuscular block may be increased and/or extended by interaction with:

- *antibiotics*, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin;
- *antiarrhythmic agents*: 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 medicines may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; the consequence of such development would be increased sensitivity to this medicine. Such medicines include various antibiotics, beta-blockers (propranolol, oxprenolol), antiarrhythmics (procainamide, quinidine), anti-rheumatic agents (chloroquine, 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 long-term anticonvulsant therapy (phenytoin, carbamazepine). Concomitant administration of other non-depolarising neuromuscular blocking agents with atracurium besilate may produce a degree of neuromuscular block in excess of that which might be expected, were an equipotent total dose of atracurium besilate administered. The degree of synergic effect may be different for various combinations of medicinal products. A depolarising muscle relaxant such as suxamethonium should not be administered to prolong neuromuscular blocking effect 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 cholinesterase inhibitors. Anticholinesterases, commonly used in the treatment of Alzheimer´s disease (e.g. donepezil), may shorten the duration or diminish the magnitude of neuromuscular blockade with atracurium besilate.

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.

As well as all neuromuscular blocking agents, this medicine should only be administered to a pregnant woman if the anticipated benefit to the mother outweighs any potential risk for the foetus.

This medicine is suitable for maintenance of muscle relaxation during caesarean section as it does not cross the placenta in clinically significant amounts following administration of recommended doses.

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

4.7 Effects on ability to drive and use machines

This precaution is not relevant to the use of atracurium. Atracurium besilate is always administered under general anaesthesia, therefore the usual precautions relating to ability to perform these activities after general anaesthesia apply.

4.8 Undesirable effects

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

The following adverse reactions presented according to the MedDRA system organ classes and MedDRA frequency convention: 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).

Very common, common and uncommon adverse reactions based on data from clinical trials. Rare and very rare adverse reactions were mostly recorded based on spontaneous reports.	
Vascular disorders	
Common	Hypotension (mild, transient)*, skin redness*
Respiratory, thoracic and mediastinal disorders	
Uncommon	Bronchospasm*
Post-Marketing Data	
Immune system disorders	
Very rare	Anaphylactic reaction, anaphylactoid reaction including shock, circulatory failure and cardiac arrest
Very rarely severe anaphylactic and anaphylactoid reactions have been reported in patients receiving atracurium besilate concomitantly with one or more anaesthetic agents.	
Nervous system disorders	
Not known	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 serious diseases predisposing to seizures, e.g. cranial trauma, cerebral oedema, viral encephalitis, hypoxic encephalopathy or uraemia. A causal relationship to laudanosine (a metabolite of atracurium besilate) has not been established. No correlation recorded between plasma laudanosine concentration and occurrence of convulsions in clinical trials.	
Skin and subcutaneous tissue disorders	
Rare	Urticaria
Musculoskeletal and connective tissue disorders	
Not known	Myopathy, muscle weakness
In severely ill ICU patients muscle weakness and myopathy have been observed following prolonged administration of muscle relaxants. The majority of these patients received concomitant corticosteroids. Causal connection with administration of atracurium besilate is not established.	

* Adverse reactions attributed to release of histamine.

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 HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

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

Therapy
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. Once the first signs of spontaneous recovery are present, recovery may be accelerated by the administration of cholinesterase inhibitors accompanied by atropine or glycopyrrolate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, other quaternary ammonium compounds
ATC code: M03AC04

Mechanism of action
Atracurium besilate is highly selective, competitive or non-depolarising blocking agent of neuromuscular transmission (neuromuscular blocking agent).

Pharmacodynamic effects
Atracurium besilate does not have direct effect on intraocular pressure and it is suitable for use in ophthalmic surgical procedures.

Paediatric population
Limited literature data indicate variability in the time of onset and duration of action of atracurium besilate in neonates as compared to children (see section 4.2).

5.2 Pharmacokinetic properties

Absorption
The plasma decay of atracurium besilate was examined as a single bolus dose, as well as a continuous IV infusion. The time of onset was approximately 2-3 minutes for atracurium, duration of action is 45 minutes.

Distribution
The plasma half-life ($T_{1/2}$) of atracurium besilate is 19.9 (±0.6) minutes and the total distribution volume (V_d) is approximately 0.16 l/kg. Atracurium besilate is 82 % bound to plasma proteins. Preliminary studies have indicated that atracurium besilate does not cross the placenta to a significant extent.

Biotransformation
Atracurium besilate inactivated on the one hand by Hofmann elimination, which is a spontaneous non-enzymatic degradation reaction occurring at physiological pH and physiological temperature, and on the other hand by enzymatic hydrolysis of ester bond catalyzed by non-specific esterases.

In experiments with blood plasma of patients with pseudocholinesterase deficit inactivation of atracurium besilate took place unchanged.

Changes of blood pH and body temperature within the physiological limits do not lead to significant changes in the duration of atracurium effect.

Elimination

Termination of neuromuscular block induced by atracurium besilate is not dependent on the hepatic or renal biotransformation or excretion. Therefore, it is unlikely that the renal, hepatic or circulatory dysfunction have an effect on duration of action.

The elimination half-life of atracurium besilate is approximately 20 minutes and the volume of distribution is 0.16 l/kg.

Haemofiltration and haemodiafiltration have a minimal effect on plasma levels of atracurium besilate and its metabolites, including laudanosine. Influence of haemodialysis and haemoperfusion on plasma levels of atracurium and its metabolites is unknown.

Concentration of metabolites is higher in ICU patients with impaired renal and/or hepatic function (see section 4.4). These metabolites do not contribute to neuromuscular block.

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.

Due to the nature of human exposure to atracurium besilate, mutagenic danger to patients undergoing surgical myorelaxation with atracurium besilate should be considered as negligible.

Carcinogenicity

Carcinogenicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzenesulfonic acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Atracurium besilate is inactivated by high pH, thus it must not be mixed in the same syringe with alkaline solutions (e.g. solutions of thiopental).
This medicine is a hypotonic solution, thus it must not be administered into the same venous access as a blood transfusion.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life before first opening
2 years.

For single use only. Once opened, the product should be used immediately.

Shelf life after dilution
Chemical and physical in-use stability has been demonstrated in Sodium Chloride Intravenous Infusion for 24 hours at 25 °C and in other common infusion fluids for 4 or 8 hours at 25 °C, respectively (see section 6.6).

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.
For storage conditions after dilution of the medicinal product, see section 6.3 and 6.6.

6.5 Nature and contents of container

2.5 ml or 5.0 ml of solution filled in 5.0 ml type I colourless borosilicate glass ampoules with break line or one point cut. Ampoules are packed in a PVC liner. Liner is placed into an outer carton.

Pack size: 1 or 5 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.

Atracurium besilate is compatible with the following infusion solutions:

Infusion solution	*Period of stability*
Sodium chloride intravenous infusion (9 mg/ml)	24 hours
Glucose intravenous infusion (50 mg/ml)	8 hours
Ringer intravenous infusion	8 hours
Sodium chloride (1.8 mg/ml) and glucose (40 mg/ml) intravenous infusion	8 hours

Ringer lactate intravenous infusion	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 25 °C.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

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Krustpils Iela 71e
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

September 2022