SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atracurium besylate 10 mg/ml injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atracurium besylate 10 mg/ml injection is a clear solution for intravenous injection in 2.5 ml, 5 ml, 10 ml and 25 ml ampoules containing 25 mg, 50 mg, 100 mg and 250 mg, respectively, of Atracurium besylate.

3 PHARMACEUTICAL FORM

Injection solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atracurium is a highly selective, competitive (non-depolarising) neuromuscular blocking agent. It is indicated:
- as an adjunct to general anaesthesia, to relax the skeletal muscles during a wide range of surgical procedures and to facilitate controlled ventilation of the lungs
- for administration by continuous infusion to maintain neuromuscular blockade during prolonged surgical procedures
- to facilitate endotracheal intubation where subsequent maintenance of neuromuscular relaxation is required
- to maintain muscular relaxation during Caesarean section

4.2 Posology and Method of Administration
Dosage of atracurium besylate should be individualised for each patient and administered by an experienced anaesthetist on the basis of body weight, sensitivity of the patient, other simultaneously used narcotics and duration of surgery. As with all neuromuscular blocking agents, monitoring of neuromuscular function is recommended during use of atracurium in order to determine the individual dosage requirements.

Atracurium besylate 10 mg/ml injection should be administered by means of intravenous injection or infusion.

*Use by intravenous injection in adults:* At the induction the recommended dose range is 0.3 -0.6 mg/kg body weight, depending on the desired duration of full block. This will provide adequate muscle relaxation for about 15 to 35 minutes.

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

Supplementary doses of 0.1 to 0.2 mg/kg may be used every 15 to 25 minutes as required to prolong full block. Successive supplementary doses do not lead to accumulation of neuromuscular blocking effect and may be administered at the end of a block (beginning of recovery).

Spontaneous recovery from the end of full block occurs in approximately 35 minutes when measured by the restoration of tetanic response to 95% of normal neuromuscular function.

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

*Use by intravenous infusion in adults:* Following an initial bolus injection of 0.3 to 0.6 mg/kg, atracurium may be administered by continuous intravenous infusion at a rate of 0.3 to 0.6 mg/kg/h (5 to 10 µg/kg/min; the usual dose is approximately 6 µg/kg/min) to maintain neuromuscular block during long surgical procedures. When necessary the dosage can be adjusted using an appropriate method, for instance the tetany response.

When possible, infusions of atracurium should be administered through a separate infusion line.

During cardiopulmonary bypass surgery, atracurium may be administered by infusion at the recommended infusion rates. If hypothermia is induced to a body temperature of 25° to 26°C, the rate of inactivation of atracurium is reduced and full neuromuscular block may be maintained by using approximately half the infusion rate required during normothermia. The usual dose is approximately 3.4 µg/kg/min.
When atracurium is diluted with the following solutions, giving concentrations of 0.5 to 0.9 mg/ml, the drug will be stable in daylight at temperatures of up to 30°C for the following time periods:

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<tr>
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<td>Intravenous Infusion</td>
<td></td>
</tr>
<tr>
<td>Compound Sodium Lactate Intravenous Infusion</td>
<td>4 h</td>
</tr>
</tbody>
</table>

Use in Neonates:
The use of this medicine 10 mg/ml is not recommended in neonates since there are insufficient data available (see section 5.1).

Use in children:
For children over the age of 1 month, the dosage is similar to that in adults on a mg per kg body weight basis.

Use in the elderly:
Atracurium besylate may be used at standard dosage, although the size of the initial dose should be at the lower end of the dose range and the drug should be administered slowly.

Use in patients with diminished renal and/or hepatic function:
Atracurium besylate may be used at standard dosage for all degrees of renal or hepatic impairment, including end stage failure of these organs.

Use in patients with cardiovascular diseases:
In patients with clinically significant cardiovascular disease, the initial dose of atracurium besylate should be administered over a period of 1 to 2 minutes.

Use in burn patients:
Patients who suffer burn injury may develop resistance to non-depolarising neuromuscular blocking drugs, including atracurium, and increased doses may be required, depending on the extent of the burn and the time elapsed since its occurrence.

Long-Term Use in Intensive Care Unit:
When there is a need for long-term controlled ventilation with use of atracurium in the Intensive Care Unit, the benefit-risk ratio of neuromuscular blockade must be considered.
Experience with muscular relaxants like atracurium in the Intensive Care Unit shows that there is a wide interpatient variability in dosage requirements and that these requirements may decrease or increase with time.
On the basis of experience with atracurium in the Intensive Care Unit, it is likely that a dose increase may be required with long-term use.
It is not known whether haemodialysis, haemoperfusion or haemofiltration influence the plasma levels of atracurium or its metabolites.
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

In common with all neuromuscular blocking agents, atracurium paralyses the respiratory as well as other skeletal muscles (e.g. muscles of arms, legs, eyelids, and mouth) without having an effect on consciousness. Consequently, the drug should be administered only with adequate anaesthesia and only by an experienced anaesthetist familiar with its pharmacological properties. All facilities for endotracheal intubation and artificial respiration should be available for immediate use.

The potential for histamine release exists in susceptible patients during administration of atracurium. Therefore, caution should be exercised when administering atracurium to patients with a history suggesting an increased sensitivity to the effects of histamine.

High rates of cross-sensitivity (greater than 50%) between neuromuscular blocking agents have been reported. Therefore, where possible, before administering atracurium, hypersensitivity to other neuromuscular blocking agents should be excluded (see section 4.3, Contra-indications). 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.

In order to avoid prolonged neuromuscular paralysis, monitoring of serial creatinine phosphokinase (CPK) values should be considered in critically ill patients in ICU receiving high dose corticosteroids (e.g. asthmatics) and who may also be considered for infusions or repeated doses of atracurium. A rise in CPK may be indicative of myonecrosis.

Atracurium does not show any significant vagal or ganglionic blocking effects in the recommended dose range. Consequently, atracurium 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 atracurium.

As with other non-depolarising neuromuscular blockers hypophosphataemia may prolong recovery. Recovery may be hastened by correcting this condition.
Atracurium besylate should be administered slowly or in divided doses over a period of 1 to 2 minutes in patients who may be especially sensitive to a decrease in arterial blood pressure, e.g. patients with hypovolaemia.

Atracurium besylate should not be mixed with thiopentone or any alkaline solutions in the same syringe since the high pH would cause inactivation of atracurium.

When a small vein is selected as the injection site, atracurium besylate (10mg/ml injection) should be flushed through the vein with physiological saline after injection. Where other (anaesthetic) drugs are administered through the same in–dwelling needle or cannula as atracurium, it is important that each drug is flushed through with physiological saline or water for injections in adequate volume. Atracurium besylate is hypotonic and must not be administered into the infusion line of a blood transfusion.

Animal studies in malignant hyperthermia in susceptible animals (Swine) and clinical studies in patients susceptible to malignant hypothermia indicate that atracurium 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 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 Undesirable Effects).

Atracurium is not recommended in children under the age of one month since not enough experience has been acquired in this age group so far.

### 4.5 Interaction with other medicinal products and other forms of interaction

The neuromuscular block produced by Atracurium Besylate 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; antiarrhythmic drugs, propranolol, calcium channel blockers, lidocaine, procainamide and quinidine; diuretics: furosemide and possibly mannitol, thiazide diuretics and acetazolamide; magnesium sulphate, 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 Besylate 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.

Administration of combinations of other non-depolarising neuromuscular blocking agents in conjunction with Atracurium Besylate may produce a degree of neuromuscular blockage in excess of that which might be expected were an equipotent total dose of Atracurium Besylate administered. Any synergistic effect may vary between different drug combinations.

Depolarising muscle relaxants, such as suxamethonium, should not be administered to prolong the neuromuscular blocking effect of non-depolarising 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 Pregnancy and lactation

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

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

Associated with the use of Atracurium Besylate there have been reports of skin flushing and mild transient hypotension or bronchospasm, which have been attributed to histamine release. Very rarely, severe anaphylactoid or anaphylactic reactions have been reported in patients receiving Atracurium Besylate in conjunction with one or more anaesthetic agents.

There have been rare 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.

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 besylate. A causal relationship has not been 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

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

Treatment: It is essential to maintain a patent 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

Atracurium is a selective, competitive (non-depolarising) neuromuscular blocking agent. It prevents neurotransmission by competition with acetylcholine for cholinergic receptor sites of the motor end-plate, but does not produce any stimulation of the muscle by itself. This results in muscle relaxation.

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 onset and duration of action of atracurium besylate are dose dependent. The effect of the recommended dose of atracurium besylate occurs within 2 minutes after administration and maximum neuromuscular blockade is usually reached within 3 to 5 minutes. Good intubation conditions are reached within 1.5 to 2 minutes in most patients. The recommended dose of 0.3 to 0.6 mg/kg for adults causes a relaxation of 15 to 35 minutes. Supplementary doses of 0.1 to 0.2 mg/kg can prolong the duration of the effect with 15 to 45 minutes. After a dose of 0.3 mg atracurium besylate per kg in humans, a plasma concentration of approximately 3 µg/ml was measured after 3 minutes.

Atracurium undergoes degradation via Hofmann elimination, a non-enzymatic breakdown process occurring at physiological pH and temperature, and also by ester hydrolysis by non-specific plasma esterases.

The duration of action of atracurium is not altered to any significant extend by variations in patient's blood pH and body temperature within the physiological range. The metabolites formed have a low activity and are produced in such small amounts that the contribution of the metabolites to the effect of atracurium can be neglected.

Atracurium produces a weak inhibition of acetylcholinesterase and butyrylcholinesterase in vitro with no clinical significance. Investigation of plasma from patients with pseudocholinesterase deficiency has shown that the inactivation of atracurium is continued unaffected.

The duration of the neuromuscular blocking effect of atracurium does not depend on metabolism and elimination by liver or kidneys. Consequently, the duration of action of atracurium besylate is not likely to be influenced by impaired renal, hepatic or circulatory function.

Plasma protein binding of atracurium besylate is 82%. Plasma proteins do not influence the rate nor the mode of atracurium besylate degradation.

The elimination half-life of atracurium besylate is between 20 and 30 minutes.

5.3 Preclinical safety data

Carcinogenicity: Carcinogenicity studies have not been performed.
Teratogenicity: Animals studies indicate that atracurium has no significant effects on foetal development.
Fertility: Fertility studies have not been performed.
Mutagenicity: Atracurium has been evaluated in short-term mutagenicity tests. It was not mutagenic in either the in vitro Ames salmonella assay at concentrations up to 1,000µg/plate or in an in vivo rat bone marrow assay at doses up to those that produced neuromuscular blockade. In a second in vitro test, the mouse lymphoma assay, mutagenicity was not observed at dose up to 60µg/ml which killed up to 50% of the treated cells. It was moderately
mutagenic at concentrations of 80µg/ml without metabolic activation and was weakly mutagenic at very high concentrations (1,200 µg/ml) when metabolising enzymes were added; at both concentrations, over 80% of the cells were killed.

In view of human exposure to atracurium, the mutagenic risk in surgical patients undergoing muscle relaxation with atracurium must be considered negligible.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Atracurium besylate 10mg/ml injection contains benzenesulfonic acid (to adjust the pH to 3.2-3.7) and water for injections. The injection does not contain any preservatives and is filled in ampoules under nitrogen atmosphere. The solution is strongly hypotonic.

6.2 Incompatibilities

Atracurium injection should not be mixed in the same syringe with thiopentone or alkaline solutions since the high pH may inactivate the drug.

6.3 Shelf life

The shelf life of Atracurium besylate 10 mg/ml injection is 1.5 year. The expiry date (month and year) is printed on the package after the words "do not use after" and on the ampoules after "Exp".

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Any unused solution in opened ampoules should be discarded immediately after use.

6.4 Special precautions for storage

The ampoules should be stored in the original packaging, protected from light, at 2 - 8°C (do not freeze). When Atracurium besylate 10 mg/ml injection is stored for one month at 25°C the loss of potency will be 5%.

Keep all medicines out of the reach of children

6.5 Nature and contents of container

Ampoules of 2.5, 5 and 10ml (both packaged per 5 or 10 pieces) containing 25, 50 and 100mg of Atracurium besylate, respectively. Ampoules of 25 ml (packaged per 2, 5 or 10 pieces) containing 250 mg of Atracurium besylate.

6.6 Instruction for Use/Handling

Finger protection should be used when ampoules are opened.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharma International Ltd
4045, Kingswood Road,
City West Business Park,
Co Dublin, Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 02848/0205
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 July 1998

10 DATE OF REVISION OF THE TEXT

23/01/2014