Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atracurium 10mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 10 mg of atracurium besilate.
Each 2.5ml ampoule contains 25mg of Atracurium Besilate
Each 5ml ampoule contains 50mg of Atracurium Besilate
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or Infusion

Clear and colourless solution

pH: 3.25 – 3.65

Osmolality: 10 – 30 mOsmol/Kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Atracurium 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

Administration by injection in adults

Route of administration: Intravenous injection or continuous infusion.

Atracurium 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 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.

Administration by infusion in adults

After an initial bolus dose of 0.3 to 0.6 mg/kg, Atracurium 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 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.

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

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

Elderly
Atracurium 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.

Reduced renal and/or hepatic function
Atracurium may be used at standard dosage at all levels of renal or hepatic function, including end stage failure.

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

Intensive care unit (ICU)

After an optional initial bolus dose of Atracurium of 0.3 to 0.6 mg/kg, Atracurium 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 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 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 paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness. Atracurium 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 administration. Caution should be exercised in administering Atracurium 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 does not have significant vagal or ganglionic blocking properties in the recommended dosage 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 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 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 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 it is important that each drug is flushed through with an adequate volume of physiological saline. Atracurium 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 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).

4.5 Interaction with other medicinal products and other forms of interactions

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

In common with all non-depolarising neuromuscular blocking agents the magnitude and/or duration of a nondepolarising 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 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 (phenytoine, carbamazepine).

The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with Atracurium may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of Atracurium 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 withatracurium.

4.6 Fertility, pregnancy and lactation

Fertility
Fertility studies have not been performed

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

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

Lactation
It is not known whether Atracurium 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 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 (#)

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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

Water for injections
Benzenesulphonic acid (for pH-adjustment)

6.2 Incompatibilities

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

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

18 months

The solution has to be used immediately after opening the container.

Shelf life after dilution

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).

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 between 2 and 8°C. Do not freeze.

Keep the container in the outer carton in order to protect from the light

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

6.5 Nature and contents of container

Box of 5 or 10 ampoules with 2.5 ml (Type I colourless glass)
Box of 5 or 10 ampoules with 5 ml (Type I colourless glass)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 medicinal product or waste material should be disposed of in accordance with local requirements.

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

Infusion Solution Stability	Period of
Sodium Chloride Intravenous Infusion BP (0.9% w/v)	24 hours
Glucose Intravenous Infusion BP (5% w/v)	8 hours
Ringer's Injection 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 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.

7 MARKETING AUTHORISATION HOLDER

Hikma Farmaceutica (Portugal), S.A.
Estrada do Rio da Mó 8, 8A e 8B - Fervença
2705-906 Terrugem SNT
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PA1217/011/001

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