Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tracrium 10 mg/ml, Solution for injection or infusion, vials

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg of Atracurium Besilate.

Each 25 ml vial contains 250 mg Atracurium Besilate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
A clear, colorless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tracrium is a highly selective, competitive or non-depolarising neuromuscular blocking agent, which is used as an adjunct to general anaesthesia to enable tracheal intubation to be performed and to relax skeletal muscles during surgery or controlled ventilation.

4.2 Posology and method of administration

Injection:
Tracrium is administered by intravenous injection. The dosage range for adults is 0.3 to 0.6 mg/kg (depending on the duration of full block required) and will provide 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:
Tracrium 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 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 Tracrium 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.

Continuous infusion:
Normothermia: After an initial bolus dose of 0.3 to 0.6 mg/kg, Tracrium can be used to maintain neuromuscular block during long surgical procedures by administration as a continuous infusion at rates of 0.3 to 0.6 mg/kg/hour.

Tracrium can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25°C to 26°C reduces the rate of inactivation of atracurium; therefore full neuromuscular blockmay be maintained by approximately half the original infusion rate at these low temperatures.

Paediatric population: The dosage in children over the age of one month is the same as that in adults on a bodyweight basis.

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

Elderly: Tracrium 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.

Renal and/or hepatic impairment: Tracrium may be used at standard dosage at all levels of renal or hepatic function, including endstage failure.

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

Monitoring: In common with all neuromuscular blocking agents monitoring of neuromuscular function is recommended during the use of Tracrium in order to individualise dosage requirements.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

In common with all the other neuromuscular blocking agents Tracrium paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness. Tracrium 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 Tracrium administration. Caution should be exercised in administering Tracrium 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.

Caution should also be exercised when administering Tracrium 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).

Tracrium does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, Tracrium 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, other forms of neuromuscular disease and severe electrolyte imbalance.

Tracrium 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.

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

When a small vein is selected as the injection site, Tracrium 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 Tracrium it is important that each drug is flushed through with an adequate volume of physiological saline.

Tracrium 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 hyperthermia indicate that Tracrium 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.

Patients with carcinomatosis especially when associated with bronchial carcinoma, may exhibit a marked sensitivity to this agent, and the neuromuscular block produced may respond poorly to neostigmine.

The neuromuscular blockage of this agent may be rapidly reversed by a cholinesterase inhibiting agent (e.g. neostigmine) in an adequate dose together with atropine as an anticholinergic agent.

Patients with severe cardiovascular disease may be more susceptible to the effects of transient hypotension. In these patients slow intravenous injection in divided doses is recommended.

Particular attention should be paid to the presence of adequate respiratory exchange, before the patient is discharged from the anaesthetist's care.

In no circumstances must Tracrium be mixed with any other intravenous administered agent. Such drugs must be adequately washed into the patient before Tracrium is administered.

Injection:
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 Tracrium is increased by the concomitant use of inhalational anaesthetics such as halothane, ether, 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
- anti-arrhythmic 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 and hexamethonium

Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to Tracrium would be consequent on such a development. Such drugs include various antibiotics, beta-blockers (propranolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), anti-rheumatic 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 anti-convulsant therapy.

The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with Tracrium may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of Tracrium administered. Any synergistic effect may vary between different drug combinations.

A depolarizing muscle relaxant such as suxamethonium chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarising agents such as atracurium as this may result in a prolonged and complex block which is difficult to reverse with anti-cholinesterase drugs.

Treatment with anti-cholinesterases, 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
Animal studies have indicated that atracurium has no significant effects on foetal development.

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

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

Breast-feeding
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 to < 1/10), uncommon (≥1/1000 to < 1/100), rare (≥1/10,000 to < 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 and Signs
Prolonged muscle paralysis and its consequences are the main signs of overdosage.

Management
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 anti-cholinesterase 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

Mechanism of action:
Tracrium is a highly selective, competitive or non-depolarising neuromuscular blocking agent.

Pharmacodynamic effects:
Tracrium has no direct effect on intra-ocular pressure, and is therefore suitable for use in ophthalmic surgery.

Spontaneous recovery from the end of full block occurs in about 35 minutes as measured by the restoration of the titanic response to 95% of normal neuromuscular function.

The neuromuscular block produced by Tracrium can be rapidly reversed by standard doses of anticholinesterase agents, such as neostigimine and edrophonium, accompanied or preceded by atropine, with no evidence of recurarisation.

The time to complete recovery is approximately 40 minutes under halothane, isoflurane or enflurane.

There is a dose-dependent relationship between increasing Tracrium dose and the amount of histamine release.

Paediatric population:
The limited data in neonates from literature reports suggests 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

Metabolism:
Tracrium is inactivated by Hoffmann elimination, a non-enzymatic process which occurs at physiological pH and temperature, and by ester hydrolysis catalysed by non-specific esterases.

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

Special patient populations:
Haemofiltration and haemodiafiltration have a minimal effect on plasma levels of atracurium and its metabolites, including laudanosine. The effects of haemodialysis and haemoperfusion on plasma levels of atracurium and its metabolites are unknown.

Elimination:
The termination of the neuromuscular blocking action of Tracrium 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.

The elimination half-life of Tracrium is approximately 20 minutes, and the volume of distribution is 0.16L/kg. Tracrium is 82% bound to plasma proteins.

5.3 Preclinical safety data

Mutagenicity:
Atracurium has been evaluated in three short-term mutagenicity tests. It was not mutagenic in either the *in vitro* Ames salmonella assay at concentrations up to 1000 micrograms/plate or in an *in vivo* rat bone marrow assay at doses up to those, which resulted in neuromuscular blockade. In a second *in vitro* test, the mouse lymphoma assay, mutagenicity was not observed at doses up to 60 micrograms/mL which killed up to 50% of the treated cells but it was moderately mutagenic at concentrations of 80 micrograms/mL in the absence of metabolising agent and weakly mutagenic at very high concentrations (1200 micrograms/mL) when metabolising enzymes were added. At both concentrations over 80% of the cells were killed.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzenesulfonic Acid Solution, used for pH adjustment only.
Water for Injections

6.2 Incompatibilities

In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products.
For further information, see section 4.4.

6.3 Shelf life

Unopened: 2 years

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 reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Please see section 6.6 for further information regarding in-use shelf life.

6.4 Special precautions for storage

Store at temperatures between 2°C and 8°C. Store in the original package in order to protect from light. Do not freeze.

Please see section 6.6 for further information regarding in-use storage precautions.

6.5 Nature and contents of container

25 ml presentations are available in Type 1, clear glass vials closed with bromobutyl rubber stopper, sealed with an aluminium collar and fitted with a plastic flip-off top.

Tracrium is available in packs containing 2 x 25 ml vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

In-use: must be used immediately. Any unused Tracrium from opened vials should be discarded immediately after use.

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

In-use following dilution: Chemical and physical in-use stability for Tracrium has been demonstrated with the following infusion solutions, for the times stated below at 30°C:

Infusion Solution	Period of Stability at 30°C
Sodium Chloride Intravenous Infusion	24 hours

British Pharmacopoeia (BP) (0.9% w/v)	
_ Glucose Intravenous Infusion British Pharmacopoeia (BP) (5% w/v)	8 hours
_ Ringer's Injection United States Pharmacopoeia (USP)	8 hours
_ Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion British Pharmacopoeia (BP)	8 hours
_ Compound Sodium Lactate Intravenous Infusion British Pharmacopoeia (BP) (Hartmann's Solution for Injection)	4 hours

Please refer to section 6.3 for microbiological in-use information.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/029/002

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