Tracrium™
Atracurium Besylate

1000000052254

QUALITATIVE AND QUANTITATIVE COMPOSITION
Ampoules 2.5ml: Each clear glass ampoule contains 25mg Atracurium Besylate in 2.5ml of a clear, faintly yellow, sterile solution.
Ampoules 5ml: Each clear glass ampoule contains 50mg Atracurium Besylate in 5ml of a clear, faintly yellow, sterile solution.
Ampoules 25ml: Each clear glass ampoule contains 250mg Atracurium Besylate in 25ml of a clear, faintly yellow, sterile solution.

PHARMACEUTICAL FORM
Injectable solution for intravenous use containing 10 mg/ml of Atracurium Besylate.

CLINICAL PARTICULARS
Therapeutic indications
Tracrium is a highly selective non-depolarising neuromuscular blocking agent. It is used in anaesthesia to facilitate tracheal intubation and as a muscle relaxant in a wide range of surgical procedures that call for controlled ventilation. Tracrium is also indicated for facilitating controlled ventilation in ICU patients.
Tracrium is suitable for the maintenance of muscle relaxation during Caesarean section.

Posology and method of administration
Tracrium is administered exclusively by intravenous injection. Tracrium should be given by slow injection to avoid any possible transitory drop in blood pressure which can sometimes follow rapid administration.
Adults
- Use as an 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 periods ranging from 15 to 35 minutes.
Full block can be prolonged with supplementary doses of 0.1 - 0.2 mg/kg as required. Successive supplementary doses do not give rise to an accumulation of neuromuscular blocking effect.
Endotracheal intubation can usually be achieved within 90 seconds of an intravenous injection of 0.5 - 0.6mg/kg.
The neuromuscular block produced by Tracrium can be rapidly reversed by standard doses of anticholinesterase agents such as neostigmine accompanied by an anticholinergic agent like atropine. 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.
- Use as an infusion
After an initial intravenous 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 0.005 to 0.01 mg/kg/min. Accurate infusion dosing can be achieved using a syringe pump.
Tracrium can be administered by infusion during cardiopulmonary by-pass surgery at the infusion rates recommended above.
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 using approximately half the original infusion rate at these low temperatures.
Tracrium is compatible with the following infusion solutions for the times stated below:

Infusion solutions	Period of stability
Physiological saline solution 0.9% w/v	24 hours
Glucose 5% w/v	8 hours
Ringer's solution	8 hours
Glucose with sodium chloride I (respectively 4.7% w/v and 0.18% w/v)	8 hours
Ringer's lactate	4 hours

Once diluted in these solutions to obtain concentrations of 0.5 to 0.9 mg/ml, the resultant Tracrium infusions will be stable in daylight at temperatures of up to 30°C.
Tracrium may also be diluted in water for injections for concentrations of 0.5 - 0.9 mg/ml but they are not recommended for infusional use. These solutions are stable for 8 hours at temperatures up to 30°C.
Use in children
Dosage in children over the age of one month is similar to that used for adults on an mg/kg bodyweight basis.
Use in the elderly
Tracrium can be used in standard doses 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 renal or hepatic insufficiency.
Tracrium can be used in standard doses in patients with renal or hepatic insufficiency.
Use in patients with severe cardiovascular disease.
In patients with clinically significant cardiovascular disease, initial doses of Tracrium should be administered slowly over a period of 60 seconds.
Use in intensive care unit (ICU) patients
After an initial intravenous dose of 0.3 - 0.6 mg/kg, Tracrium can be used to maintain neuromuscular block by administration as a continuous infusion at rates of 11-13 mcg/kg/min (0.65 - 0.78 mg/kg/hr). There may be a wide inter-patient variability in dosage requirements (from 4.5 mcg/kg/min to 29.5 mcg/kg/min). Available data suggest that the requirement for Tracrium may increase during the course of prolonged administration in ICU. This is more common in patients who develop peripheral oedema.
The rate of spontaneous recovery from neuromuscular block (TOF>0.75) after an infusion of Tracrium is independent of the duration of administration. Spontaneous recovery can be expected to occur in approximately 60 minutes (range 32 - 108 min).

Contraindications
Atracurium is contraindicated in patients known to be hypersensitive to Atracurium, cisatracurium or benzenesulfonic acid or to any of the excipients.

Warnings and Precautions
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.
Caution should also be exercised when administering Atracurium to patients who have shown hypersensitivity to other neuromuscular blocking agents since cross-sensitivity between neuromuscular blocking agents has been reported (*see Contraindications*). 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, other forms of neuromuscular disease and severe electrolyte imbalance.
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 thiopentone 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 hyperthermia 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 Adverse Reactions*).

Interactions
The neuromuscular block produced by Atracurium 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, lignocaine, procainamide and quinidine.
- Diuretics: frusemide 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 would be consequent on such a development. Such drugs include various antibiotics, beta-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.
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 drug combinations.
A depolarising 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 can be difficult to reverse with anti-cholinesterase drugs.

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.

Ability to perform tasks that require judgement, motor or cognitive skills
No data.

Adverse Reactions
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
Events which have been attributed to histamine release are indicated by a hash (#).
Common: Hypotension (mild, transient)#, Skin flushing#

Respiratory, thoracic and mediastinal disorders
Events which have been attributed to histamine release are indicated by a hash (#).
Uncommon: Bronchospasm#

Postmarketing Data
Immune system disorders
Very rare: Anaphylactic reaction, anaphylactoid reaction.
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.

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.

Overdosage
Symptoms and Signs
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.

PHARMACEUTICAL PARTICULARS
List of excipients
Benzenesulphonic acid at 32% w/v qs at pH 3.2-3.7; water for Injections BP

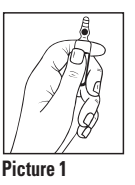
Incompatibilities
TRACRIUM should not be mixed in the same syringe as thiopental or any other alkaline substance as the high pH deactivates it.

Shelf life
The expiry date is indicated on the packaging.

Special precautions for storage
Store between 2°C and 8°C.
Protect from light.
Do not freeze.
Open and unused vials should be discarded.
Short periods at temperatures up to 30°C are permissible but ONLY to allow transportation or temporary storage outside of a cold store. It is estimated that an 8% loss of potency would occur if Atracurium injection was stored at 30°C for 1 month.

Instructions for use and handling
See "Posology and method of administration".

Instructions to open the ampoule
Ampoules are equipped with the OPC (One Point Cut) opening system and must be opened following the below instructions:
- hold with the hand the bottom part of the ampoule as indicated in picture n. 1
- put the other hand on the top of the ampoule positioning the thumb above the coloured point and press as indicated in picture n. 2


Picture 1


Picture 2

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THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.

GlaxoSmithKline