

Tracrium*

Injection

GlaxoWellcome

To the Medical and Pharmaceutical Professions

Presentations

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. (not available in IRAN)

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.

Dosage and administration

Use by injection in adults

Tracrium is administered by intravenous injection. The dosage range for adults is 0.3 to 0.6mg/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 0.6mg/kg.

Full block can be prolonged with supplementary doses of 0.1 to 0.2mg/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 **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.

Use as an infusion in adults

After an initial bolus dose of 0.3 to 0.6mg/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 0.6mg/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° 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.

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

Infusion Solution	Period of Stability
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 besylate concentrations of 0.5mg/ml and above, the resultant solutions will be stable in daylight for the stated periods at temperatures of up to 30°C.

Use in children

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

Use in the 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.

Use in patients with reduced renal and/or hepatic function

Tracrium may be used at standard dosage at all levels of renal or hepatic function, including endstage failure.

Use in patients with 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.

Contra-indications

Tracrium should not be administered to patients known to have an allergic hypersensitivity to the drug.

Precautions/warnings

In common with all 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. In common with other neuromuscular blocking agents, 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.

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.

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.

Mutagenicity

Atracurium has been evaluated in 3 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 which resulted in neuromuscular blockade. In a second *in vitro* test, the mouse lymphoma assay, mutagenicity was not observed at doses up to 60µg/ml which killed up to 50% of

the treated cells, but it was moderately mutagenic at concentrations of 80µg/ml in the absence of metabolising agent and weakly mutagenic at very high concentrations (1,200µg/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.

Carcinogenicity

Carcinogenicity studies have not been performed.

Teratogenicity

Animal studies have indicated that **Tracrium** has no significant effects on foetal development.

Fertility

Fertility studies have not been performed.

Pregnancy and lactation

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.

It is not known whether **Tracrium** is excreted in human milk.

Adverse reactions

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

Drug interactions

The neuromuscular block produced by **Tracrium** 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 **Tracrium** 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 **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 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.

Overdosage

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 precautions and recommendations

Storage precautions

Store at temperatures between 2° and 8°C.

Protect from light.

Do not freeze.

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 **Tracrium** Injection was stored at 30°C for one month. Any unused Tracrium from opened ampoules should be discarded.

Further information

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

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.

Tests with plasma from patients with low levels of pseudocholinesterase show that the inactivation of **Tracrium** proceeds unaffected. **Tracrium** has no direct effect on intra-ocular pressure, and is therefore suitable for use in ophthalmic surgery.

Variations in the blood pH and body temperature of the patient within the physiological range will not significantly alter the duration of action of **Tracrium**.

Long-term use in the Intensive Care Unit (ICU)

Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the risk benefit ratio of neuromuscular blockade must be considered.

For **Tracrium**, as with other neuromuscular blocking agents used in intensive care units, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that **Tracrium** infusion requirements may increase with prolonged administration in the ICU. The effects of haemodialysis, haemoperfusion and haemofiltration on plasma levels of atracurium and its metabolites are unknown.

One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. No pharmacological effect of laudanosine have been demonstrated in humans, even after days/weeks of prolonged infusion.

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

This is 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 experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

*Trade mark