

NEW ZEALAND DATA SHEET

1. TRACRIUM (atracurium besilate 10 mg/mL injections (2.5 mL and 5.0 mL))

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 mL ampoule contains 25 mg atracurium besilate, each 5 mL ampoule contains 50 mg atracurium besilate.

TRACRIUM 2.5 mL and 5.0 mL injections contain no preservative.

3. PHARMACEUTICAL FORM

TRACRIUM injection is a clear, faintly yellow, sterile, aqueous solution in a glass ampoule containing 10 mg/mL atracurium besilate.

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, and to facilitate mechanical ventilation in Intensive Care Unit (ICU) patients.

4.2 Dose and method of administration

Use in adults

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.

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.

Infusion

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 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 British Pharmacopoeia (BP) (0.9 %w/v)	24 hours
Glucose Intravenous Infusion 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 BP	8 hours
Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution for Injection)	4 hours

When diluted in these solutions to give atracurium besilate concentrations of 0.5 mg/mL and above, the resultant solutions will be stable in daylight for the stated periods at temperatures 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 a 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 end stage 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.

Use in intensive care unit (ICU) patients

After an optional initial bolus dose of TRACRIUM of 0.3 to 0.6 mg/kg, TRACRIUM can be used to maintain neuromuscular block by administering a continuous infusion at rates between 11 and 13 µg/kg/min (0.65 to 0.78 mg/kg/hr). However there is a wide inter-patient variability in dosage requirements. Dosage requirements may change with time. Infusion rates as low as 4.5 µg/kg/min (0.27 mg/kg/hr) or as high as 29.5 µg/kg/min (1.77 mg/kg/hr) are required in some patients.

The rate of spontaneous recovery from neuromuscular block after infusion of TRACRIUM 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 TRACRIUM in order to individualise dosage requirements.

4.3 Contraindications

TRACRIUM 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 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.

Caution should also be exercised when administering atracurium 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, Contraindications).

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.

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, Undesirable Effects).

Other

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 1000 µg/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 80 µg/mL in the absence of metabolising agent and weakly mutagenic at very high concentrations (1200 µg/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.

4.5 Interaction with other medicines and other forms of interaction

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, 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), 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 neuro-muscular 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 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 Fertility, pregnancy and lactation

Fertility

Fertility studies have not been performed.

Pregnancy

Animal studies have indicated that TRACRIUM 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.

Lactation

It is not known whether TRACRIUM 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

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ 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

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#

Post-marketing Experience

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 (eg 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 TRACRIUM and a causal relationship has not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Signs

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

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

TRACRIUM is a highly selective, competitive or non-depolarising neuromuscular blocking agent.

TRACRIUM has no direct effect on intraocular pressure, and is therefore suitable for use in ophthalmic surgery.

5.2 Pharmacokinetic properties

Metabolism

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.

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

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.

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 atracurium is approximately 20 minutes, and the volume of distribution is 0.16 L/kg. Atracurium is 82% bound to plasma proteins.

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.

Concentrations of metabolites are higher in ICU patients with abnormal renal and/or hepatic function (see section 4.4, Special warnings and precautions for use). These metabolites do not contribute to neuromuscular block.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzenesulfonic acid, water for injection.

6.2 Incompatibilities

No data available.

6.3 Shelf life

24 months from the date of manufacture.

6.4 Special precautions for storage

Store at 2 to 8°C (Refrigerate, do not freeze). Protect from light.

Short periods at temperatures up to 25°C are permissible but ONLY to allow transportation or temporary storage outside of a cold store. It is estimated that an 5% loss of potency would occur if TRACRIUM injection was stored at 25°C for one month.

TRACRIUM contains no preservative. Any unused TRACRIUM from opened ampoules should be discarded.

6.5 Nature and contents of container

25 mg in 2.5 mL ampoules: boxes of 5
50 mg in 5.0 mL ampoules: boxes of 5

6.6 Special precautions for disposal (and other handling)

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
P O Box 62027
Sylvia Park
AUCKLAND 1644

9. DATE OF FIRST APPROVAL

20 November 2013

10. DATE OF REVISION OF THE TEXT

May 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
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All sections revised	Update to the SPC-style format
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