TRACRIUM

Atracurium besylate

Injection 10mg/ml

00002_0000074818

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Injection:

A sterile solution containing 10 mg atracurium besylate per mL, without an antimicrobial preservative, supplied in ampoules.

2. PHARMACEUTICAL FORM

Solution for injection or infusion.

3. CLINICAL PARTICULARS

3.1 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. *TRACRIUM* injection is also used to be performed and to relax skeletal muscles during surgery or controlled ventilation, and to facilitate mechanical ventilation in Intensive Care Unit (ICU) patients.

3.2 Dosage and Administration

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

• Use by injection in adults

TRACRIUM is administered by intravenous (i.v.) 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 i.v. 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.

• Use as an infusion in adults

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/h.

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 *TRACRIUM*, therefore full neuromuscular block may be maintained by approximately half the original infusion rate at these low temperatures.

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

Infusion Solution	Period of Stability
Sodium Chloride i.v. Infusion British Pharmacopoeia (BP) (0.9% w/v)	24 hours
Glucose i.v. 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) i.v. Infusion BP	8 hours
Compound Sodium Lactate i.v. Infusion BP (Hartmann's Solution for Injection)	4 hours

When diluted in these solutions to give *TRACRIUM* 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.

• Use in children

The dosage in children over the age of 1 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 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 of between 11 and 13 micrograms/kg/min (0.65 to 0.78 mg/kg/h). However, there is wide inter-patient variability in dosage requirements. Dosage requirements may change with time. Infusion rates as low as 4.5 micrograms/kg/min (0.27 mg/kg/h) or as high as 29.5 micrograms/kg/min (1.77 mg/kg/h) 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 greater than 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.

3.3 Contraindications

TRACRIUM is contraindicated in patients known to be hypersensitive to atracurium, cisatracurium or benzenesulfonic acid.

3.4 Warnings and Precautions

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.

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 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 *TRACRIUM* 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.

Whenever the use of *TRACRIUM* or any neuromuscular blocking agent is contemplated in the ICU, it is recommended that neuromuscular transmission be monitored continuously during administration with the help of nerves stimulator.

Additional doses of *TRACRIUM* or any other neuromuscular blocking agent should not be given before there is a definite response to T or first twitch, if no response is elicited, infusion administration should be discontinued until a response returns.

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 *TRACRIUM*, a causal relationship to laudanosine has not been established (*see Adverse Reactions*).

3.5 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
- 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, 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 depolarising muscle relaxant such as suxamethonium chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarising agents such as *TRACRIUM*, 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.

3.6 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.

Lactation

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

3.7 Effects and Ability to Drive and Use Machines

This precaution is not relevant to the use of *TRACRIUM. TRACRIUM* will always be used in combination with a general anaesthetic and therefore the usual precautions relating to performance of tasks following general anaesthesia apply.

3.8 Adverse Reactions

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.

2D Datamatrix N° XXXX

2D Datamatrix N° XXXX

ASPEN Artwork Panel

AW Version: 2	**Page:** 1 of 2
New Item Code: 00002_0000074818	
Previous Item Code: N/A	
Market Indonesia	
Number of Colours: 1	
BLACK	
Manufacturing Site: Aspen Small Volume Parenteral	
Drawing Reference: SVP-PI-002	
Drawing Version: 01	
Originated by: Sami Hajredin	
Originated at: ASPEN Dandenong	
Originated on: 17-MAR-2021	
Amended on: 15-APR-2021	

150 mm Measuring Bar

ASPEN Artwork Panel • August 2019 • Version 7

DISETUJUI OLEH BPOM : 29/11/2021

ID : EREG100028VR12100005
EREG100028VR12100006

2D Datamatrix N° XXXX

2D Datamatrix N° XXXX

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 Data

Immune system disorders

Very rare Anaphylactic reaction, anaphylactoid reaction

Very rarely, severe anaphylactoid or anaphylactic reactions have been reported in patients receiving *TRACRIUM* 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.

3.9 Overdose

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.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamics

Mechanism of Action

Atracurium 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.

4.2 Pharmacokinetics

Metabolism

Atracurium 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 atracurium 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 atracurium.

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

Injection:

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 Warnings and Precautions*). These metabolites do not contribute to neuromuscular block.

Pre-Clinical 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 *TRACRIUM*, the mutagenic risk to patients undergoing surgical relaxation with *TRACRIUM* must be considered negligible.

Carcinogenicity

Carcinogenicity studies have not been performed.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Benzenesulphonic Acid Solution

Water for Injections

5.2 Shelf-Life

24 months.

5.3 Special Precaution for Storage

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

Store at temperatures between 2°C and 8°C.

Protect from light.

Do not freeze.

Any unused *TRACRIUM* injection from opened ampoules should be discarded.

5.4 Nature and Contents of Container

As registered locally

5.5 Incompatibilities

No data.

5.6 Use and Handling

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

Infusion Solution	Period of Stability
Sodium Chloride i.v. Infusion BP (0.9% w/v)	24 hours
Glucose i.v. Infusion BP (5% w/v)	8 hours
Ringer's Injection USP	8 hours
Sodium Chloride (0.18% w/v) and Glucose (4% w/v) i.v. Infusion BP	8 hours
Compound Sodium Lactate i.v. Infusion BP (Hartmann's Solution for Injection)	4 hours

When diluted in these solutions to give *TRACRIUM* besylate 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.

Packaging

Box, 5 ampoules @ 2.5 mL, Reg.No.

Box, 5 ampoules @ 5 mL, Reg.No

HARUS DENGAN RESEP DOKTER

Made by Aspen SVP (Pty) Ltd
Port Elizabeth, South Africa

Imported by:
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia

PI based on GDS19/IPI06 (03 June 2013)

00002_0000074818

ASPEN Artwork Panel

AW Version: 2	**Page:** 2 of 2
New Item Code: 00002_0000074818	
Previous Item Code: N/A	
Market Indonesia	
Number of Colours: 1	
BLACK	
Manufacturing Site: Aspen Small Volume Parenteral	
Drawing Reference: SVP-PI-002	
Drawing Version: 01	
Originated by: Sami Hajredin	
Originated at: ASPEN Dandenong	
Originated on: 17-MAR-2021	
Amended on: 15-APR-2021	

150 mm Measuring Bar

ASPEN Artwork Panel • August 2019 • Version 7

DISETUJUI OLEH BPOM : 29/11/2021

ID : EREG100028VR12100005
EREG100028VR12100006