1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

TRACRIUM® Injection 2,5 ml (solution for injection)

TRACRIUM® Injection 5,0 ml (solution for injection)

COMPOSITION:

Each ampoule of 2,5 ml contains 25 mg atracurium besylate.

Each ampoule of 5,0 ml contains 50 mg atracurium besylate.

Excipients:

Benzene sulphonic acid and water for injections.

PHARMACOLOGICAL CLASSIFICATION:

A 17.1 Peripherally-acting muscle relaxants

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

TRACRIUM is a selective, competitive (non-depolarising) neuromuscular blocking agent.

Pharmacokinetic properties:

TRACRIUM is degraded mainly by spontaneous non-enzymatic decomposition (Hofmann elimination) which occurs at body pH and temperature into inactive metabolites. The termination of the neuromuscular blocking action of TRACRIUM is not dependent on

metabolism and excretion by the liver or kidneys. The duration of action is therefore unlikely to be affected by impaired renal, hepatic or circulatory function. Variations in the blood pH and body temperature of the patient within the pathological range may alter the duration of action of TRACRIUM. It is possible that some decomposition may occur by non-specific plasma esterases. Tests with plasma from patients with low levels of cholinesterase show that the inactivation of TRACRIUM proceeds unaffected. TRACRIUM has no effect on the intra-ocular pressure.

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 WARNINGS AND SPECIAL PRECAUTIONS).

INDICATIONS:

TRACRIUM is used in anaesthesia to relax skeletal muscles and to facilitate controlled ventilation. TRACRIUM is suitable for endotracheal intubation especially where subsequent muscle relaxation is required.

CONTRA-INDICATIONS:

Known hypersensitivity to atracurium besylate.

WARNINGS AND SPECIAL PRECAUTIONS:

TRACRIUM PARALYSES THE RESPIRATORY MUSCLES AS WELL AS OTHER SKELETAL MUSCLES, BUT HAS NO EFFECT ON CONSCIOUSNESS. THEREFORE IT SHOULD BE ADMINISTERED ONLY WITH ADEQUATE ANAESTHESIA AND ONLY BY OR UNDER THE CLOSE SUPERVISION OF AN ANAESTHETIST AND ADEQUATE

FACILITIES MUST BE AVAILABLE FOR ENDOTRACHEAL INTUBATION AND ARTIFICIAL VENTILATION.

MONITORING OF NEUROMUSCULAR BLOCKADE IS RECOMMENDED DURING THE USE OF TRACRIUM IN ORDER TO INDIVIDUALISE DOSAGE REQUIREMENTS.

The potential exists for histamine release in susceptible patients. Caution should be exercised in administering TRACRIUM to patients with a history suggestive of an increased sensitivity to the effects of histamine.

TRACRIUM should be used with caution in patients with myasthenia gravis, other neuromuscular diseases and severe electrolyte disorders in which potentiation of other non-depolarising agents has been noted.

Resistance to non-depolarising neuromuscular blocking agents may develop in burn patients. Increased doses of non-depolarising muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.

In limited clinical studies, in patients susceptible to malignant hyperthermia, TRACRIUM has not triggered this syndrome.

TRACRIUM is hypotonic and must not be administered into the infusion line of a blood transfusion.

Intensive Care Unit (ICU) Patients:

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.

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.

INTERACTIONS:

The neuromuscular block produced by TRACRIUM may be increased by the concomitant use of inhalation anaesthetics such as halothane, isoflurane and enflurane.

The neuromuscular block produced by TRACRIUM may be increased by the concomitant use of:

- antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin
- antiarrhythmic drugs: propranolol, calcium channel blockers, lignocaine, procainamide and quinidine
- diuretics: furosemide and possibly mannitol, thiazide diuretics and acetazolamide
- magnesium sulphate
- ketamine
- lithium salts
- ganglion blocking agents: trimetaphan, hexamine.

Certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to TRACRIUM would be consequent on such 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-depolarizing agents such as TRACRIUM, as this may result in a prolonged and complex block which can be difficult to reverse with anti-cholinesterase drugs.

PREGNANCY AND LACTATION:

Use in pregnancy and obstetrics:

Safety during the course of pregnancy has not been established. 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 into human milk.

DOSAGE AND DIRECTIONS FOR USE:

Use by Injection:

TRACRIUM is administered by intravenous injection. It must not be mixed with thiopentone or any alkaline agents as the high pH would cause inactivation of the TRACRIUM. Where a small vein is selected as the injection site, TRACRIUM should be
flushed through the vein with physiological saline after injection. Where 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 physiological saline.

The dosage range recommended for adults is 0,3 to 0,6 mg/kg depending on the duration of complete neuromuscular block (full block) required and will provide muscle relaxation for 15 to 35 minutes. Complete neuromuscular block (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. Endotracheal intubation can usually be accomplished within 90 seconds from the intravenous injection of 0,5 to 0,6 mg/kg. The neuromuscular block produced by TRACRIUM can be rapidly reversed by standard doses of anti-cholinesterase agents such as neostigmine and edrophonium preceded or accompanied by atropine, with no evidence of recurarization. Recovery from the end of complete neuromuscular block (full block) without use of neostigmine occurs in about 35 minutes as measured by restoration of the tetanic response to 95% of normal neuromuscular function.

Use in 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/hr (0,005 to 0,01 mg/kg/minute). Accurate dosage administration of the infusion may be achieved using a syringe pump. 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, 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 BP (0,9 % m/v)	24 hours
Glucose Intravenous BP (5 % m/v)	8 hours
Ringers Injection USP	8 hours
Sodium Chloride (0,18 % m/v) and Glucose (4 % m/v)	

Intravenous Infusion BP 8 hours

Compound Sodium Lactate Intravenous Infusion BP

(Hartmann's Solution) 4 hours

When diluted in these solutions to give atracurium concentrations of 0,5 mg/ml to 0,9 mg/ml, infusions of TRACRIUM are stable in daylight at temperatures of up to 30 °C.

Dosage in children:

The dosage requirements in children aged one month and over are similar to those in adults on a mg/kg basis.

Dosage in Elderly and High risk Patients:

TRACRIUM may be used at standard dosage in elderly patients and in those with cardiac, respiratory, renal (including end-stage failure) or hepatic failure. 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. Patients with clinically significant cardiovascular disease may be more susceptible to the effects of transient hypotension. In these patients slow intravenous injection in divided doses over a period of 1-2 minutes is recommended. 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.

Long-term use in Intensive Care Units (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. 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.

SIDE EFFECTS:

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 and by vagal stimulation during surgery. There have been reports of skin flushing, instances of transient hypotension and bronchospasm, which may be due to histamine release. Anaphylactoid reactions have also been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 anti-cholinesterase agents accompanied by atropine or glycopyrrolate, once evidence of spontaneous recovery is present.

IDENTIFICATION:

2,5 ml and 5,0 ml ampoules containing a clear faint yellow solution for intravenous administration.

PRESENTATION:

Box of 5 x Ampoules of 2,5 ml.

Box of 5 x Ampoules of 5,0 ml.

STORAGE INSTRUCTIONS:

Keep out of reach of children.

Store between 2 °C and 8 °C. Do not freeze.

Protect from light.

Open ampoules of TRACRIUM should be discarded immediately after use.

REGISTRATION NUMBER:

TRACRIUM Injection 2,5 ml: R/17.1/209

TRACRIUM Injection 5,0 ml: R/17.1/210

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PACKAGE INSERT:

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