

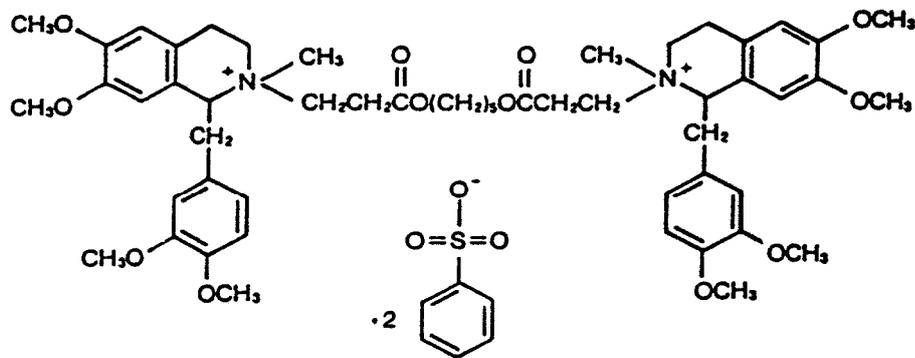
## PRODUCT INFORMATION

### TRACRIUM® INJECTION (atracurium besylate)

**NAME OF THE DRUG:** atracurium besylate

#### DESCRIPTION:

TRACRIUM (atracurium besylate) is an intermediate-duration, non-depolarising, skeletal muscle relaxant for intravenous administration. TRACRIUM is chemically unique, and is designated as 2,2'-(3,11-dioxo-4,10-dioxatridecamethylene)-bis-(2-methyl-1,2,3,4-tetrahydropapaverinium benzenesulfonate). It has a molecular weight of 1243.49, and its empirical formula is  $C_{53}H_{72}N_2O_{12} \cdot 2C_6H_5O_3S$ . The structural formula is:



CAS 64228-81-5

TRACRIUM Injection is a sterile solution in water. Each mL contains 10 mg atracurium besylate. The pH is adjusted to 3.2-3.7 with benzenesulfonic acid.

#### PHARMACOLOGY:

Non-depolarising agents antagonise the neurotransmitter action of acetylcholine by binding competitively with cholinergic receptor sites on the motor end-plate. This antagonism is inhibited and neuromuscular block reversed, by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

The duration of neuromuscular blockade produced by TRACRIUM is approximately one third to one half the duration seen with d-tubocurarine and pancuronium at equipotent doses. As with other non-depolarising neuromuscular blockers, the time to onset of paralysis decreases and the duration of maximum effect increases with increasing TRACRIUM doses.

The ED<sub>95</sub> (dose required to produce 95% suppression of the muscle twitch response) averages 0.23 mg/kg. An initial TRACRIUM dose of 0.4 to 0.5 mg/kg generally produces maximum neuromuscular blockade within 3 to 5 minutes of injection, with suitable intubation conditions within 2 to 2.5 minutes. Recovery from neuromuscular blockade (under balanced anaesthesia) can be expected to begin approximately 20 to 35 minutes after injection. Recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and

recovery is usually 95% complete 60 to 70 minutes after injection. The neuromuscular blocking action of TRACRIUM is enhanced in the presence of potent inhalation anaesthetics. Isoflurane and enflurane increase the potency of TRACRIUM and prolong neuromuscular blockade by approximately 35%; however, halothane's potentiating effect (approximately 20%) is marginal (see **DOSAGE AND ADMINISTRATION** section).

Repeat administration of maintenance doses of TRACRIUM has no cumulative effect on the duration of neuromuscular blockade; therefore, doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.4 to 0.5 mg/kg under balanced anaesthesia, the first maintenance dose (suggested maintenance dose is 0.08 to 0.10 mg/kg) is generally required within 20 to 45 minutes, and subsequent maintenance doses are usually required at approximately 15 to 25 minute intervals. Repeated bolus dosing with atracurium does not give rise to prolongation of the neuromuscular blocking effect. This is reflected in the lack of accumulation.

Once recovery from TRACRIUM's neuromuscular blocking effects begins, it proceeds more rapidly than recovery from d-tubocurarine, alcuronium and pancuronium. Regardless of TRACRIUM dose, the time from start of recovery (from complete block) to complete recovery, as measured by restoration of the tetanic response to 95% of normal, is approximately 30 minutes under balanced anaesthesia, and approximately 40 minutes under halothane, enflurane or isoflurane. Repeated doses have no cumulative effect on recovery rate.

Reversal of neuromuscular blockade produced by TRACRIUM can be achieved with an anticholinesterase agent such as neostigmine, edrophonium, or pyridostigmine, in conjunction with an anticholinergic agent such as atropine. Under balanced anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after an initial TRACRIUM dose of 0.5 to 0.6 mg/kg, or approximately 10 to 30 minutes after 0.08 to 0.10 mg/kg maintenance dose, when recovery of muscle twitch has started. Complete reversal is usually accomplished within 8-10 minutes of the administration of reversing agents. There have been few reports of recurarization following reversal of TRACRIUM-induced neuromuscular blockade, a finding consistent with the rapid elimination of TRACRIUM.

The pharmacokinetics of TRACRIUM in man are essentially linear within the 0.3 to 0.6 mg/kg dose range. The elimination half-life is approximately 20 minutes. THE DURATION OF NEUROMUSCULAR BLOCKADE PRODUCED BY TRACRIUM DOES NOT CORRELATE WITH PLASMA PSEUDOCHOLINESTERASE LEVELS AND IS NOT ALTERED BY THE ABSENCE OF RENAL FUNCTION. This is consistent with the results of *in vitro* studies which have shown that TRACRIUM is inactivated in plasma via two nonoxidative pathways: ester hydrolysis, catalyzed by nonspecific esterases; and Hofmann elimination, a nonenzymatic chemical process which occurs at physiological pH and body temperature. The rate of Hofmann elimination, which is the principal route of elimination for TRACRIUM is increased at a higher pH or at higher temperatures and reduced at a lower pH or lower temperatures. Some placental transfer occurs in humans.

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.

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

The termination of the neuromuscular blocking action of TRACRIUM is not dependent on hepatic or renal function. 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 Uks. Atracurium is 82% bound to plasma proteins.

Radiolabel studies demonstrated that TRACRIUM undergoes extensive degradation in cats, and that neither kidney nor liver plays a major role in its elimination. Biliary and urinary excretion were the major routes of excretion of radioactivity (totalling 90% of the labelled dose within 7 hours of dosing), of which TRACRIUM represented only a minor fraction. The metabolites in bile and urine were similar, including products of Hofmann elimination and ester hydrolysis. A major metabolite is laudanosine which has the potential to accumulate in patients with end-stage liver failure who have received atracurium by infusion for several days to weeks. Laudanosine does not possess any neuromuscular blocking activity; CNS activating properties have been demonstrated in animals. Laudanosine is probably metabolised in the liver and is also cleared to a relatively small extent through the kidney. Accumulation is more likely in patients with hepatic and renal failure.

Plasma histamine levels were increased by 15% in a dose-dependent way with initial TRACRIUM doses up to 0.5 mg/kg, and haemodynamic changes were minor within this dose range. Histamine levels increased by 92% following 0.6 mg/kg of TRACRIUM and were shown to correlate with a transient (5 minutes) decrease in blood pressure and a brief (2 to 3 minutes) episode of skin flushing. While these effects are of little clinical significance in most patients, the possibility of substantial histamine release at recommended doses in sensitive individuals or in patients in whom substantial histamine release would be especially hazardous (e.g. patients with significant respiratory or cardiovascular disease) must be considered.

It is not known whether the prior use of other non-depolarising neuromuscular blocking agents has any effect on the activity of TRACRIUM. The prior use of suxamethonium decreases by approximately 2 to 3 minutes the time to maximum blockade induced by TRACRIUM, and may increase the depth of blockade.

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

#### **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.

#### **CONTRAINDICATIONS:**

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

## **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 ANAESTHESIA OR SEDATION/ANALGESIA IN THE ICU AND ONLY BY THOSE SKILLED IN THE MANAGEMENT OF ARTIFICIAL RESPIRATION AND ONLY WHEN FACILITIES ARE INSTANTLY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND FOR PROVIDING ADEQUATE VENTILATION OF THE PATIENT, INCLUDING THE ADMINISTRATION OF OXYGEN UNDER POSITIVE PRESSURE AND THE ELIMINATION OF CARBON DIOXIDE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION AND ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

TRACRIUM HAS THE POTENTIAL TO CAUSE HISTAMINE RELEASE. ANAPHYLACTIC AND ANAPHYLACTOID REACTIONS HAVE BEEN REPORTED AND HAVE SOMETIMES BEEN LIFE-THREATENING. FOR THIS REASON IT IS ESSENTIAL THAT APPROPRIATE RESUSCITATIVE EQUIPMENT BE IMMEDIATELY AVAILABLE. CAUTION SHOULD BE EXERCISED IN ADMINISTERING TRACRIUM TO PATIENTS WITH A HISTORY SUGGESTIVE OF AN INCREASED SENSITIVITY TO THE EFFECTS OF HISTAMINE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

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

TRACRIUM has no known effect on consciousness, pain threshold, or cerebation.

TRACRIUM Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, TRACRIUM may be inactivated and a free acid may be precipitated.

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**).

Although TRACRIUM is a less potent histamine releaser than d-tubocurarine, the possibility of histamine release in sensitive individuals must be considered. Special caution should be exercised in administering TRACRIUM to patients in whom substantial histamine release would be especially hazardous (e.g. patients with clinically significant cardiovascular or respiratory disease) and in patients with any history (e.g. severe anaphylactoid reactions) suggesting a greater risk of histamine release. In these patients, the recommended initial TRACRIUM dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Limited clinical experience indicates that mean arterial pressure decreases in a substantial percentage of patients with a history of cardiovascular disease even at these doses.

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 may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of non-depolarising agents has been noted. A reduced dosage of TRACRIUM and the use of a peripheral nerve stimulator for assessing neuromuscular blockade is especially important in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of TRACRIUM has not been established in patients with bronchial asthma.

TRACRIUM does not have significant vagal or ganglion 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.

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.

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.

Multiple factors in anaesthetic practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anaesthetic agents and suxamethonium are recognised as the principal pharmacological triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognise and treat MH in any patient scheduled for general anaesthesia. Reports of MH have been rare in cases in which TRACRIUM has been used. In a clinical study of MH-susceptible patients, TRACRIUM did not trigger this syndrome.

One of the major metabolites of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with transient hypotension and cerebral excitatory effects. Long-term atracurium administration may result in plasma laudanosine concentrations similar to those that produced seizure-like activity in rabbits. Although seizures have been seen in ICU patients receiving atracurium, definite causality has not been attributable to laudanosine or atracurium. These patients usually had predisposing causes (such as cranial trauma, cerebral oedema, hypoxic encephalopathy, viral encephalitis, uraemia).

### **Interactions with other drugs:**

TRACRIUM (atracurium besylate) is potentiated by isoflurane and by enflurane anaesthesia, and marginally potentiated by halothane (see **DOSAGE AND ADMINISTRATION** section).

In common with other 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.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

The prior administration of suxamethonium does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by TRACRIUM. As with other non-depolarising neuromuscular blocking agents, it is advisable to await evidence of recovery from suxamethonium-induced neuromuscular block before administering TRACRIUM.

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.

### **Use in Pregnancy: (Category C)**

Atracurium has been shown to cross the placenta to a limited degree although the transfer of metabolites may be greater. Animal studies of teratogenic potential are limited to a single study in which pregnant rabbits received subcutaneous doses of 0.15 mg/kg once daily or 0.1 mg/kg twice daily during the period of organogenesis. There was no clear evidence of teratogenic activity at these doses, which are less than those used clinically, although there was some indication of fetotoxicity manifest as slight increases in the incidences of minor skeletal and visceral anomalies. There are no adequate and well controlled studies in pregnant women. In common with all neuromuscular blocking agents, TRACRIUM should be used in pregnant women only if in the opinion of the physician, the potential benefit outweighs any potential risk to the foetus.

### **Use in Obstetrics:**

In an open study, TRACRIUM was administered (0.3 mg/kg) to 26 pregnant women during delivery by Caesarean section. No harmful effects were attributable to TRACRIUM in any of the newborn infants, although TRACRIUM was shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following Caesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulphate, the reversal of neuromuscular blockade may be unsatisfactory and TRACRIUM dose should be lowered as indicated.

### **Use in Lactation:**

It is not known whether atracurium or its metabolites are excreted in milk of humans or animals. Because many drugs are excreted in human milk, caution should be exercised when TRACRIUM is administered to a nursing woman.

### **Use in Children:**

Safety and effectiveness in paediatric patients below the age of one month have not been established. No dosage adjustments are required for paediatric patients two years of age or older. Refer to **DOSAGE AND ADMINISTRATION** for recommendations of dose in patients between the ages of 1 month and 2 years.

### **ADVERSE REACTIONS:**

In common with most neuromuscular blocking agents the potential exists for histamine release in susceptible patients. In clinical trials involving 875 patients there were reports of skin flushing ranging from 1% at doses less than 0.3 mg/kg to 29% at doses of 0.6 mg/kg or greater, and transient hypotension ranging from 1% to 14% respectively for the corresponding dosages. Bronchospasm and rarely anaphylactoid reactions have also been reported.

In a large scale muscle relaxant surveillance study in which 3,782 patients were treated with TRACRIUM, adverse reactions considered possibly or probably related to TRACRIUM were observed in approximately 10% of patients. Localised skin reactions, generalised flushing and hypotension each occurred in approximately 2 to 3% of patients. Hypertension, tachycardia and bradycardia were observed with an incidence of approximately 1%. Bronchospasm was observed in approximately 0.4% of patients.

There have been infrequent 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). In clinical trials no correlation was apparent between plasma laudanosine concentration and the occurrence of seizures. There have been reports of muscle weakness following prolonged use of muscle relaxants in severely ill patients in the ICU. This has very rarely been seen in association with TRACRIUM and a causal relationship has not been established.

Based on clinical practice experience in approximately 11 million patients who received TRACRIUM, spontaneously reported adverse reactions were uncommon. The following adverse reactions are among the most frequently reported, but there are insufficient data to support an estimate of their incidence:

General: allergic reactions (anaphylactic or anaphylactoid responses) which, in rare instances, were severe (e.g. cardiac arrest).

Musculoskeletal: inadequate block.

Cardiovascular: hypotension, vasodilatation (flushing), tachycardia, bradycardia.

Respiratory: dyspnoea, bronchospasm, laryngospasm.

Integumentary: rash, urticaria, reactions at injection site.

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.

## **DOSAGE AND ADMINISTRATION:**

To avoid distress to the patient, TRACRIUM should not be administered before unconsciousness has been induced. TRACRIUM should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g. barbiturate solutions).

TRACRIUM should be administered intravenously. **DO NOT GIVE TRACRIUM INTRAMUSCULARLY.** Intramuscular administration of TRACRIUM may result in tissue irritation and there is no clinical data to support this route of administration.

### **Bolus doses for intubation and maintenance of neuromuscular blockade**

#### **Use in adults:**

The initial dosage for adults ranges from 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.

A TRACRIUM dose of 0.5 to 0.6 mg/kg (2.2 to 2.6 times the ED<sub>95</sub>), given as an intravenous bolus injection provides suitable conditions for non-emergency intubation in 2 to 2.5 minutes in most patients which is comparable to other drugs of this class. Maximum neuromuscular blockade is achieved approximately 2 to 5 minutes after injection. Complete neuromuscular blockade generally lasts 20 to 35 minutes under balanced anaesthesia. Recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually complete 60 to 70 minutes after injection.

TRACRIUM is potentiated by isoflurane or enflurane anaesthesia. The same initial TRACRIUM dose of 0.5 to 0.6 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if TRACRIUM is first administered under steady state of isoflurane or enflurane, the initial TRACRIUM dose may be reduced by approximately one-third, i.e. 0.3 to 0.4 mg/kg, to adjust for the potentiating effects of these anaesthetic agents. With halothane, which has only a marginal (approximately 20%) potentiating effect on TRACRIUM, smaller dosage reductions may be considered.

TRACRIUM doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial TRACRIUM injection, but the need for maintenance doses should be determined by clinical criteria. Because TRACRIUM lacks cumulative effects, maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anaesthesia, slightly longer under isoflurane or enflurane. Higher TRACRIUM doses (up to 0.2 mg/kg) permit maintenance dosing at longer intervals.

#### **Use in children:**

No TRACRIUM dosage adjustments are required for paediatric patients two years of age or older. A TRACRIUM dose of 0.4 mg/kg is recommended as the initial dose for paediatric patients aged 1 month to 2 years of age under halothane anaesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Safety and efficacy in children younger than one month have not been established.

In common with all neuromuscular blocking agents monitoring of neuromuscular function is recommended, particularly during long-term use, in order to individualise dosage requirements.

### **Special considerations:**

TRACRIUM may be used at standard dosage at all levels of renal or hepatic function, including end stage failure.

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.

An initial TRACRIUM dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease (an increased incidence of hypotensive episodes has been seen in these patients) and for patients with any history (e.g. anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. There has been no clinical experience with TRACRIUM in these patients, and no specific dosage adjustments can be recommended.

An initial TRACRIUM dose of 0.3 to 0.4 mg/kg is recommended following the use of suxamethonium for intubation under balanced anaesthesia. Further reductions may be desirable with the use of potent inhalation anaesthetics. The patient should be permitted to recover from the effects of suxamethonium prior to TRACRIUM administration.

### **Reversal:**

Reversal of neuromuscular blockade produced by TRACRIUM can be achieved with an anticholinesterase such as neostigmine in conjunction with an anticholinergic agent such as atropine. Under balanced anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after the initial TRACRIUM dose or approximately 10 to 30 minutes after a maintenance dose, when recovery of muscle twitch has started. Complete reversal is usually accomplished within 8 to 10 minutes of the administration of reversing agents. Rare instances of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacological antagonism of TRACRIUM-induced neuromuscular blockade. As with other agents in this class, the tendency for residual neuromuscular block is increased if reversal is attempted at deep levels of blockade or if inadequate doses of reversal agents are employed.

### **Use as an Infusion:**

An initial bolus dose of 0.3 to 0.6 mg/kg of TRACRIUM can be used to maintain neuromuscular block during long surgical procedures by administration as a continuous infusion. An initial infusion rate of 9 to 10 µg/kg/min may be required to restore adequate neuromuscular block. Thereafter, a rate of 5 to 9 µg/kg/min should be adequate to maintain continuous neuromuscular block in the range of 89 to 99% in most paediatric and adult patients under balanced anaesthesia. Occasional patients may require infusion rates as low as 2 µg/kg/min or as high as 15 µg/kg/min.

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 degrees C reduces the rate of inactivation of atracurium, therefore full neuromuscular block may be maintained by approximately half the original infusion rate at these temperatures.

TRACRIUM Injection 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
Ringers Injection USP Sodium Chloride (0.18% w/v) and Glucose (4% w/v)	8 hours
Intravenous Infusion BP Compound Sodium Lactate Intravenous Infusion, BP	8 hours
(Hartmann's Solution for injection)	4 hours

When diluted in these solutions to give atracurium 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 25°C.

**Longer term use in Intensive Care Unit (ICU) Patients:**

There is only limited information on the efficacy and safety of long-term (median duration approximately 90 hours) intravenous atracurium infusion to facilitate mechanical ventilation in the ICU (n=58).

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 µg/kg/min (0.65 - 0.78 mg/kg/hr). However, there is 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 32-108 minutes has been observed in clinical trials.

Limited information is available on the plasma levels or clinical consequences of atracurium metabolites that may accumulate during days to weeks of atracurium administration in ICU patients. Laudanosine, a major biologically active metabolite of atracurium without neuromuscular blocking activity, produces transient hypotension and, in higher doses, cerebral excitatory effects (generalised muscle twitching and seizures) when administered to several animal species. Although seizures have been seen in ICU patients receiving atracurium, definite causality has not been attributable to laudanosine or atracurium. These

patients usually had predisposing causes (such as cranial trauma, cerebral oedema, hypoxic encephalopathy, viral encephalitis, uraemia).

### **Monitoring:**

In common with all neuromuscular blocking agents continuous monitoring of neuromuscular function is recommended during the use of TRACRIUM in order to individualise dosage requirements which may be variable over time.

### **OVERDOSAGE:**

There has been limited experience with TRACRIUM overdose. The possibility of iatrogenic overdose can be minimised by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of TRACRIUM can be expected to produce enhanced pharmacological effects. Overdosage may increase the risk of histamine release and cardiovascular effects, especially hypotension. If cardiovascular support is necessary, this should include proper positioning, fluid administration, and the use of vasopressor agents if necessary. The patient's airway should be maintained, with manual or mechanical ventilation as necessary. A longer duration of neuromuscular blockade may result from overdose and a peripheral nerve stimulator should be used to monitor recovery. Full sedation will be required since consciousness is not impaired. Recovery may be facilitated by administration of an anti-cholinesterase reversing agent such as neostigmine, edrophonium or pyridostigmine, in conjunction with an anticholinergic agent such as atropine.

### **Further Information:**

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.

### **PRESENTATION:**

TRACRIUM Injection, 10 mg atracurium besylate in each mL.

Ampoules of 2.5 mL and 5 mL. Packs of 5 ampoules.

### **Storage:**

Store under refrigeration at 2°C to 8°C.

DO NOT FREEZE. PROTECT FROM LIGHT.

Any unused TRACRIUM from opened ampoules should be discarded.

**NAME AND ADDRESS OF THE SPONSOR:**

GlaxoSmithKline Australia Pty Ltd  
1061 Mountain Highway  
Boronia Victoria 3155

Marketed in New Zealand by:  
GlaxoSmithKline NZ Ltd  
Auckland, New Zealand.

®TRACRIUM is a registered trade mark of the GlaxoSmithKline group of companies.

**DATE OF TGA APPROVAL:** 8 January 1996

**SAFETY RELATED NOTIFICATION:** 10 November 2008

Issue No. 8