NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Atracurium Besylate Injection

10 mg/mL

Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Atracurium Besylate Injection contains atracurium besilate 10 mg, in each mL.

The solution also contains benzenesulfonic acid to adjust the pH.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DBL™ Atracurium Besylate Injection is a clear, colourless or faint yellow, sterile solution for injection

The pH is adjusted between 3.2 to 7.7.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL™ Atracurium Besylate Injection is indicated as an adjunct to general anaesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

4.2 Dose and method of administration

DBL™ Atracurium Besylate Injection should only be administered intravenously. ***Do not give DBL™ Atracurium Besylate Injection intramuscularly*** since this may result in tissue irritation and there are no clinical data to support this route of administration.

To avoid distress to the patient, DBL™ Atracurium Besylate Injection should not be administered before unconsciousness has been induced. DBL™ Atracurium Besylate Injection should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (eg barbiturate solutions).

To accurately monitor the degree of muscle relaxation and to minimise the possibility of overdose, the use of a peripheral nerve stimulator is recommended to monitor muscle twitch suppression and recovery in patients using DBL™ Atracurium Besylate Injection during anaesthesia.

Initial bolus doses for intubation

An atracurium besilate dose of 0.4 to 0.5 mg/kg (1.7 to 2.2 times the ED_{95}), given as an intravenous bolus injection, is the recommended initial dose for most patients. Following this dose, suitable conditions for non-emergency intubation can be expected within 2 to 2.5 minutes in most patients which is comparable to other drugs of this class. Maximum neuromuscular blockade is generally achieved approximately 3 to 5 minutes after administration. Under balanced anaesthesia, this initial dose usually results in complete neuromuscular blockade for about 20 to 35 minutes. Spontaneous recovery to 25% of control is generally achieved approximately 35 to 45 minutes after administration and complete recovery is usually achieved within 60 to 70 minutes after administration.

Although atracurium is potentiated by isoflurane or enflurane anaesthesia, the same initial atracurium besilate dose (0.4 to 0.5 mg/kg) may be used for intubation if given prior to the administration of these inhalation agents. However if the initial atracurium dose is administered after steady state anaesthesia with isoflurane or enflurane has been achieved, the dose should be reduced by approximately one-third, ie to 0.25 to 0.35 mg/kg. Smaller dosage reductions may be considered with concomitant halothane anaesthesia since it has only a marginal (approximately 20%) potentiating effect on atracurium.

Maintenance doses - intermittent IV injection

During prolonged surgical procedures neuromuscular blockade may be maintained with atracurium besilate maintenance doses of 0.08 to 0.10 mg/kg. The first maintenance dose will generally be required 20 to 45 minutes after the initial atracurium dose, but the need for maintenance doses should be determined by the individual patient's requirements and response. Since atracurium lacks cumulative effects, maintenance doses may be administered at relatively regular intervals, ranging from approximately 15 to 25 minutes for patients under balanced anaesthesia. Slightly longer intervals may be required for maintenance doses when isoflurane or enflurane are used for anaesthesia, or when higher atracurium besilate maintenance doses (up to 0.2 mg/kg) are used.

Reversal of neuromuscular blockade

The neuromuscular blockade induced by atracurium can be reversed with an anticholinesterase agent such as neostigmine or pyridostigmine, usually in conjunction with an anticholinergic agent such as atropine to prevent the adverse muscarinic effects of the anticholinesterase. Under balanced anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after the initial atracurium dose, or approximately 10 to 30 minutes after the last atracurium maintenance dose, when recovery of muscle twitch has started. Complete reversal of neuromuscular blockade is usually achieved within 8 to 10 minutes after administration of the reversing agents.

Rare instances of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacological antagonism of atracurium 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.

Dosage adjustments

The initial atracurium besilate dose should be reduced to 0.3 to 0.4 mg/kg and given slowly or in divided doses over one minute in patients with significant cardiovascular disease, since the incidence of hypotensive episodes may increase in these patients. Similar dosage adjustments are recommended for patients with any history suggesting a greater risk of histamine release (eg history of severe anaphylactoid reactions or asthma).

Dosage reductions should also be considered 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 atracurium in these patients, and therefore no specific dosage adjustments can be recommended.

For paediatric patients 2 years or older, no atracurium dosage adjustments are required. A dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anaesthesia. Maintenance doses may be required with slightly greater frequency in paediatric patients.

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

Atracurium 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.

Following the use of suxamethonium for endotracheal intubation under balanced anaesthesia, the initial atracurium besilate dose should be reduced to 0.3 to 0.4 mg/kg. Further reductions may be necessary when potent inhalation anaesthetics are used concomitantly. These doses should not be administered until the patient has recovered from the neuromuscular blocking effects of suxamethonium.

Use as an infusion

After the initial atracurium bolus dose, neuromuscular blockade may be maintained in adults and children aged 2 or more years during prolonged surgical procedures, by administering atracurium besilate as a continuous intravenous infusion at a rate of 0.3 to 0.6 mg/kg/hour.

The infusion should be individualised for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation. Accurate dosing is best achieved using a precision infusion pump.

The infusion should not be commenced until early spontaneous recovery from the initial atracurium bolus dose is evident. An initial infusion rate of 9 to 10 micrograms/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 micrograms/kg/min should be adequate to maintain continuous neuromuscular block in the range of 89 to 99% in most pediatric and adult patients under balanced anesthesia. Occasional patients may require infusion rates as low as 2 micrograms/kg/min or as high as 15 micrograms/kg/min.

Atracurium besilate infusion solutions may be prepared by admixing DBL™ Atracurium Besylate Injection with an appropriate diluent (see below) to give an atracurium besilate

concentration of 0.5 mg/mL to 5 mg/mL. The administration of the diluted product should commence as soon as practicable after the dilution.

The neuromuscular blocking effect of atracurium administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of atracurium should, therefore, be considered for patients receiving inhalation anesthesia. The rate of atracurium besilate infusion should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane anesthesia; smaller reductions should be considered in the presence of halothane.

DBL™ Atracurium Besylate Injection can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25 to 28°C reduces the rate of inactivation of atracurium, and therefore full neuromuscular block may be maintained with approximately half the original infusion rate at these temperatures.

Spontaneous recovery from neuromuscular block following discontinuation of atracurium besilate infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

The amount of infusion solution required per minute will depend upon the concentration of atracurium in the infusion solution, the desired dose of atracurium and the patient's weight. The following tables provide guidelines for delivery in mL/hr (equivalent to microdrops/min when 60 microdrops = 1 mL), of atracurium solutions in concentrations of 0.2 mg/mL (20 mg in 100 mL) or 0.5 mg/mL (50 mg in 100 mL) with an infusion pump or a gravity flow device.

Atracurium Besilate Infusion Rates for a Concentration of 0.2 mg/mL									
Patient Weight (Kg)	Drug Delivery Rate (micrograms/kg/min)								
	5	6	7	8	9	10	11	12	13
	Infusion Delivery Rate (mL/hr)								
30	45	54	63	72	81	90	99	108	117
35	53	63	74	84	95	105	116	126	137
40	60	72	84	96	108	120	132	144	156
45	68	81	95	108	122	135	149	162	176
50	75	90	105	120	135	150	165	180	195
55	83	99	116	132	149	165	182	198	215
60	90	108	126	144	162	180	198	216	234
65	98	117	137	156	176	195	215	234	254
70	105	126	147	168	189	210	231	252	273
75	113	135	158	180	203	225	248	270	293
80	120	144	168	192	216	240	264	288	312
90	135	162	189	216	243	270	297	324	351
100	150	180	210	240	270	300	330	360	390

Atracurium Besilate Infusion Rates for a Concentration of 0.5 mg/mL									
Patient Weight (Kg)	Drug Delivery Rate (micrograms/kg/min)								
	5	6	7	8	9	10	11	12	13
	Infusion Delivery Rate (mL/hr)								
30	18	22	25	29	32	36	40	43	47
35	21	25	29	34	38	42	46	50	55
40	24	29	34	38	43	48	53	58	62
45	27	32	38	43	49	54	59	65	70
50	30	36	42	48	54	60	66	72	78
55	33	40	46	53	59	66	73	79	86
60	36	43	50	58	65	72	79	86	94
65	39	47	55	62	70	78	86	94	101
70	42	50	59	67	76	84	92	101	109
75	45	54	63	72	81	90	99	108	117
80	48	58	67	77	86	96	106	115	125
90	54	65	76	86	97	108	119	130	140
100	60	72	84	96	108	120	132	144	156

Compatibility

DBL™ Atracurium Besylate Injection diluted to 0.5 mg/mL with the following infusion solutions, and stored at 30°C, was shown to be stable for the times stated below.

Infusion Solution	Period of stability
Sodium Chloride 0.9% Intravenous Infusion	24 hours
Glucose 5% Intravenous Infusion	24 hours
Glucose 4% and Sodium Chloride 0.18% Intravenous Infusion	24 hours
Ringer's Injection USPCompound Sodium Lactate	24 hours
Intravenous Infusion (Hartmann's Solution for Injection)	4 hours

DBL™ Atracurium Besylate Injection diluted to 5 mg/mL with the following infusion solutions, and stored at 30°C in 50 mL plastic syringes, was shown to be stable for the times stated below.

Infusion Solution	Period of stability
Sodium Chloride 0.9% Intravenous Infusion	24 hours
Glucose 5% Intravenous Infusion	24 hours
Glucose 4% and Sodium Chloride 0.18% Intravenous Infusion	24 hours
Ringer's Injection USP	24 hours
Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution for Injection)	8 hours

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 to 8°C for not more than 24 hours.

4.3 Contraindications

DBL™ Atracurium Besylate Injection is contraindicated in patients known or suspected to have a hypersensitivity to the product. DBL™ Atracurium Besylate Injection should not be used on a long-term basis (eg continuous use over a period of days) for maintenance intubation and muscle paralysis in tetanus, chest trauma, etc. Serum laudanosine levels may accumulate in these situations and therefore may increase the potential for causing CNS excitation.

4.4 Special warnings and precautions for use

DBL™ Atracurium Besylate Injection should be used only by those skilled in the management of artificial respiration and only when facilities are immediately available for endotracheal intubation and for providing adequate ventilation support, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or control ventilation, and anticholinesterase agents should be immediately available for reversal of neuromuscular blockade.

Like certain other agents used during anaesthesia, atracurium has the potential to cause histamine release and therefore, there is a possibility of life-threatening anaphylactic reactions. For this reason it is essential that appropriate resuscitative equipment be immediately available.

Although atracurium is a less potent histamine releaser than tubocurarine, the possibility of histamine release in sensitive individuals must be considered. Special caution should be taken if administering DBL™ Atracurium Besylate Injection to patients in whom substantial histamine release would be especially hazardous (eg patients with clinically significant cardiovascular or respiratory disease) and in patients with any history suggesting a greater risk of histamine release (eg history of severe anaphylactoid reactions or asthma). The initial atracurium besilate dose recommended in these patients 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. However, even at these doses, limited clinical experience indicates that mean arterial pressure decreases in a substantial percentage of patients with a history of cardiovascular disease.

Atracurium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anaesthesia.

Do not give DBL™ Atracurium Besylate Injection by intramuscular administration.

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

When a small vein is selected as the injection site, DBL™ Atracurium Besylate Injection should be flushed through the vein with physiological saline after injection. When other anaesthetic drugs are administered through the same indwelling needle or cannula as DBL™ Atracurium Besylate Injection, it is important that each drug is flushed through with an adequate volume of physiological saline.

Atracurium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarising agents has been noted. A reduced dosage of atracurium 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 atracurium has not been established in patients with bronchial asthma.

Atracurium does not have significant vagal or ganglion blocking properties in the recommended dosage range. Consequently, atracurium will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery. Therefore, bradycardia during anaesthesia may be more common with atracurium than with other muscle relaxants.

Atracurium should be administered over a period of 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, eg those who are hypovolaemic.

As with other nondepolarising neuromuscular blocking agents, resistance to atracurium may develop in patients suffering from burns. Such patients may require increased doses of atracurium depending on the time elapsed since the burn injury and the extent of the burn.

Long-term use in Intensive Care Unit (ICU)

When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information available on the efficacy and safety of long-term (days to weeks) administration of atracurium intravenous infusions to facilitate mechanical ventilation in ICU. These data suggest that there is wide interpatient variability in dosage requirements and that these requirements may decrease or increase with time.

Little 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 species of animals. There have been rare reports of seizures in ICU patients who have received atracurium or other agents. These patients usually had predisposing causes (such as head trauma, cerebral oedema, hypoxic encephalopathy, viral encephalitis, uraemia). There are insufficient data to determine whether or not laudanosine contributes to seizures in ICU patients.

The rate of spontaneous recovery from neuromuscular block in ICU patients is independent of the duration of atracurium administration. Clinical trials have demonstrated that following the discontinuation of atracurium infusion in ICU patients, spontaneous recovery of four twitches in a train-of-four occurred between 15 and 75 minutes, with an average of approximately 30 minutes and spontaneous recovery to a train-of four ratio >75% (the ratio of the height of the fourth to the first twitch in a train-of-four) occurred between 32 and 108 minutes, with an average of approximately 60 minutes.

Whenever the use of atracurium or any neuromuscular blocking agent is contemplated in ICU, it is recommended that neuromuscular transmission be monitored continuously during administration with the help of a nerve stimulator. Additional doses of atracurium or any other neuromuscular blocking agent should not be given before there is a definitive twitch response. If no response is elicited, infusion administration should be discontinued until a response returns.

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

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

Paediatric population

Safety and effectiveness in children below the age of 1 month have not been established.

4.5 Interaction with other medicines and other forms of interaction

As with other nondepolarising neuromuscular blocking agents, the magnitude and/or duration of atracurium's effects may be increased as a result of an interaction with the following agents.

Inhalation anaesthetics: atracurium is potentiated by isoflurane and enflurane anaesthesia, and only marginally potentiated by halothane anaesthesia (see section 4.2).

Antibiotics: including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin, clindamycin and vancomycin.

Antiarrhythmic drugs: lignocaine, procainamide, quinidine.

Beta-Blockers: propranolol.

Calcium channel blockers: verapamil.

Diuretics: frusemide, thiazides, acetazolamide and possibly mannitol.

Ganglion blocking agents: trimetaphan, hexamethonium.

Others: magnesium sulfate, ketamine, lithium salts, and quinine.

It is not known whether the prior use of other nondepolarising neuromuscular blocking agents has any affect on the activity of atracurium. The prior use of suxamethonium reduces the onset (to maximum blockade) by approximately 2 to 3 minutes, and may increase the depth of neuromuscular blockade induced by atracurium. Therefore, atracurium should not be administered until the patient has recovered from suxamethonium induced neuromuscular blockade. If suxamethonium is used to prolong the neuromuscular blocking effects of atracurium, this may result in a prolonged and complex block which can be difficult to reverse with anticholinesterase drugs. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome. Such drugs include various antibiotics, *beta*-blockers (propranolol, oxprenolol), antiarrhythmic drugs (procainamide, quinidine), antirheumatic drugs (chloroquine, d-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium. In these situations a consequent increased sensitivity to atracurium would be expected.

The onset of neuromuscular blockade is likely to be lengthened and the duration of blockade shortened in patients receiving chronic anticonvulsant therapy (eg carbamazepine, phenytoin).

4.6 Fertility, pregnancy and lactation

Fertility

Fertility studies have not been performed.

Pregnancy

Category C. Atracurium crosses the placenta, but there have been no demonstrated adverse effects in the foetus or newborn infant. Atracurium has been shown to be potentially teratogenic at up to half the human dose when given to nonventilated rabbits by the subcutaneous route at sub-paralyzing doses. Therefore, atracurium should not be used during pregnancy unless, in the opinion of the physician, the potential benefits outweigh the unknown hazards.

Use in obstetrics

It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the foetus or increase the likelihood that

resuscitation of the newborn infant will be necessary. The possibility that a forceps delivery will be necessary may increase.

In an open study, atracurium besilate (0.3 mg/kg) was administered to 26 pregnant women during delivery by caesarean section. No harmful effects were attributable to atracurium in any of the newborn infants, although small amounts of atracurium were 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 sulfate, the reversal of neuromuscular blockade may be unsatisfactory and the atracurium dose should be lowered as indicated.

Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DBL™ Atracurium Besylate Injection is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

During extensive clinical trials atracurium was well tolerated and produced few adverse reactions. As with most neuromuscular blocking agents, the potential exists for adverse reactions suggestive of histamine release in susceptible patients.

The table below includes all adverse reactions reported attributable to atracurium during clinical trials.

PERCENT OF PATIENTS REPORTING ADVERSE REACTIONS				
Body system	Initial Atracurium Besilate Dose (mg/kg)			
Adverse reaction	0.00-0.30	0.31-0.50*	≥0.60	Total
Nervous system				
Skin flush	1.0%	8.7%	29.2%	5.0%
Respiratory system				
Wheezing/Bronchial secretions	0.2%	0.3%	0%	0.2%
Skin and appendages				
Erythema	0.6%	0.5%	0%	0.6%
Itching	0.4%	0%	0%	0.2%
Hives	0.2%	0%	0%	0.1%

* Includes the recommended initial dosage range for most patients.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. The table below summarises the incidences of substantial vital sign changes noted during atracurium clinical trials, in patients without cardiovascular disease, in whom these parameters were assessed.

PERCENT OF PATIENTS SHOWING ≥30% VITAL SIGN CHANGES FOLLOWING ADMINISTRATION OF ATRACURIUM				
Vital sign change	Initial Atracurium Besilate Dose (mg/kg)			
	0.00-0.30	0.31-0.50*	≥0.60	Total
Mean arterial pressure				
Increase	1.9%	2.8%	0%	2.1%
Decrease	1.1%	2.1%	14.3%	1.9%
Heart rate				
Increase	1.6%	2.8%	4.8%	2.1%
Decrease	0.8%	0%	0%	0.6%

* Includes the recommended initial dosage range for most patients.

Other adverse reactions which have been reported during clinical trials include:

Respiratory system

Bronchospasm

Cardiovascular system

Tachycardia

Body as a whole

Anaphylactoid reactions have been reported rarely.

In large scale atracurium surveillance studies, adverse reactions considered possibly or probably related to atracurium were observed in approximately 10% of patients. These include:

Cardiovascular system

Generalised flushing and hypotension each occurred in approximately 2 to 3% of patients. Hypertension, tachycardia and bradycardia were observed in approximately 1% of patients.

Skin and appendages

Localised skin reactions occurred in approximately 2 to 3% of patients.

Respiratory system

Bronchospasm was reported in approximately 0.4% of patients.

The following adverse reactions have been reported during clinical practice for atracurium. Although these are the most frequently reported spontaneous adverse events, their frequency is classified as uncommon (approximately 0.01 to 0.02%). There are insufficient data to support an estimate of their incidence.

Body as a whole

Allergic reactions (ie anaphylactic or anaphylactoid responses), reaction at injection site.

Nervous system

Inadequate block, prolonged block.

There have been rare reports of seizures in ICU patients following long-term infusion of atracurium to support mechanical ventilation. There are insufficient data to define the contribution, if any, of atracurium and/or its metabolite laudanosine (see section 4.4).

Cardiovascular system

Hypotension, hypertension, vasodilatation (flushing), tachycardia, bradycardia.

There have been rare instances of severe allergic reactions eg cardiac arrest.

Respiratory system

Dyspnoea, bronchospasm, laryngospasm, wheezing, hypoxaemia.

Skin and appendages

Rash, urticaria, generalised erythema, angioneurotic oedema.

Musculoskeletal system

Muscle weakness and/or myopathy following prolonged use of muscle relaxants in severely ill patients in the ICU.

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

There is limited experience with atracurium overdosage following parenteral administration. The possibility of iatrogenic overdosage can be minimised by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of atracurium are likely to produce symptoms consistent with extensions of the usual pharmacological effects. Overdosage may increase the risk of histamine release and adverse 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 maintained as necessary. The duration of neuromuscular blockade may be prolonged 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 the administration of an anticholinesterase agent such as neostigmine or pyridostigmine, in conjunction with an anticholinergic agent such as atropine.

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

Mechanism of action

Atracurium besilate is a nondepolarising neuromuscular blocking agent with an intermediate duration of action, administered intravenously to produce skeletal muscle relaxation.

Nondepolarising neuromuscular blocking agents antagonise the action of the neurotransmitter acetylcholine by competitively binding with cholinergic receptor sites on the motor endplate of the myoneural junction. These effects may be inhibited or reversed by the administration of anticholinesterases such as neostigmine or pyridostigmine.

The duration of neuromuscular blockade produced by equipotent doses of atracurium is approximately one-third to one-half that induced by tubocurarine and pancuronium, but similar or slightly longer than that induced by vecuronium. As with other nondepolarising neuromuscular blocking agents, the time to onset of paralysis is reduced, and the duration of maximum effect prolonged, with increasing atracurium doses.

The ED_{95} (dose required to produce 95% suppression of the muscle twitch response) averages 0.23 mg/kg. An initial atracurium besilate dose of 0.4 to 0.5 mg/kg generally produces maximum neuromuscular blockade within 3 to 5 minutes of administration, with suitable intubation conditions achieved within 2 to 2.5 minutes. Recovery from neuromuscular blockade (under balanced anaesthesia) can be expected to begin approximately 20 to 35 minutes after administration of atracurium. Recovery to 25% of control is achieved approximately 35 to 45 minutes after administration, and recovery is usually 95% complete within 60 to 70 minutes after administration.

The neuromuscular blocking effects of atracurium are enhanced in the presence of potent inhalation anaesthetics. For example, isoflurane and enflurane increase the potency of atracurium and prolong neuromuscular blockade by approximately 35%. However, halothane has only a marginal potentiating effect (approximately 20%) on the action of atracurium (see section 4.2).

Repeated administration of atracurium maintenance doses 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 atracurium besilate dose of 0.4 to 0.5 mg/kg under balanced anaesthesia, the first maintenance dose (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.

Once recovery from atracurium's neuromuscular blocking effects begins, it proceeds more rapidly than recovery from tubocurarine, alcuronium, and pancuronium. Regardless of the atracurium 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 anaesthesia. Repeated doses have no cumulative effect on recovery rate.

Reversal of the neuromuscular blocking effects produced by atracurium can be achieved with an anticholinesterase agent such as neostigmine 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 atracurium besilate dose of 0.4 to 0.5 mg/kg, or approximately 10 to 30 minutes after a maintenance dose of 0.08 to 0.10 mg/kg, when recovery of muscle twitch has started. Complete reversal is usually accomplished within 8 to 10 minutes after administration of the reversing agents.

Rare cases of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacological antagonism of atracurium 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of atracurium besilate in humans are essentially linear within the dose range of 0.3 to 0.6 mg/kg. The elimination half-life is approximately 20 minutes. *The duration of neuromuscular blockade produced by atracurium 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 atracurium is inactivated in plasma via two nonoxidative pathways: ester hydrolysis, catalysed 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 atracurium, 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.

Radiolabel studies demonstrated that atracurium undergoes extensive degradation in cats, and that neither the renal nor hepatic routes play 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 atracurium 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 accumulates during long-term use (ie over a period of days) and has CNS activating properties. In normal use, the levels of laudanosine obtained do not produce any significant pharmacological effects.

The effects of haemodialysis, haemoperfusion and haemofiltration on plasma levels of atracurium and its metabolites are unknown.

With initial atracurium besilate doses up to 0.5 mg/kg, plasma histamine levels were shown to increase by 15% in a dose dependent way, but haemodynamic changes were minor within this dose range. Following the administration of 0.6 mg/kg of atracurium besilate, histamine levels were shown to increase by 92%, 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 must be considered in sensitive individuals, or in patients in whom substantial histamine release would be especially hazardous (eg patients with significant respiratory or cardiovascular disease).

It is not known whether the prior use of other nondepolarising neuromuscular blocking agents has any affect on the activity of atracurium. The prior use of suxamethonium reduces the onset (to maximum blockade) by approximately 2 to 3 minutes, and may increase the depth of neuromuscular blockade induced by atracurium (see section 4.5).

5.3 Preclinical safety data

Genotoxicity

Mutagenicity tests showed that atracurium was non-mutagenic in both the Ames Salmonella assay (at concentrations up to 1000 micrograms/plate) and in a rat bone marrow cytogenicity assay (at up to paralysing doses). A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 micrograms/mL, in the absence of metabolic activation) which killed over 80% of the treated cells. There was no mutagenicity at 60 micrograms/mL and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 micrograms/mL and higher) which also killed over 80% of the treated cells.

Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Carcinogenicity

Carcinogenesis studies have not been performed.

Reproductive and developmental toxicity

Fertility studies have not been performed.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

- Benzenesulfonic acid
- Water for injections

6.2 Incompatibilities

No data available.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

DBL™ Atracurium Besylate Injection should be stored at 2 to 8°C. Do not freeze. Protect from light. Any unused atracurium besilate from opened ampoules should be discarded.

6.5 Nature and contents of container

	Strength	Pack Size
DBL™ Atracurium Besylate Injection	25 mg/2.5 mL	5 ampoules, glass
DBL™ Atracurium Besylate Injection	50 mg/5 mL	5 ampoules, glass

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
PO Box 3998
Auckland, New Zealand, 1140
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

03 May 2001

10. DATE OF REVISION OF THE TEXT

13 February 2019

Summary table of changes

Section changed	Summary of new information
All	New Data Sheet format in accordance with Medsafe guidance