1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

NIMBEX 2 mg/ml (2,5 ml) Injection

NIMBEX 2 mg/ml (5 ml) Injection

NIMBEX 2 mg/ml (10 ml) Injection

NIMBEX 5 Injection

COMPOSITION

Each NIMBEX 2 mg/ml (2,5 ml) ampoule contains cisatracurium 2 mg/ml, as the besylate.

Each NIMBEX 2 mg/ml (5 ml) ampoule contains cisatracurium 2 mg/ml, as the besylate.

Each NIMBEX 2 mg/ml (10 ml) ampoule contains cisatracurium 2 mg/ml, as the besylate.

Each NIMBEX 5 vial contains cisatracurium 5 mg/ml, as the besylate.

PHARMACOLOGICAL CLASSIFICATION

A 17.1 Peripherally-acting muscle relaxants

PHARMACOLOGICAL ACTION:

Cisatracurium is an intermediate-duration, non-depolarising benzylisoquinolinium skeletal muscle relaxant. Cisatracurium binds to cholinergic receptors on the motor-end-plate to antagonise the action of acetylcholine, resulting in a competitive block of neuromuscular transmission. This action is readily reversed by anticholinesterase agents such as neostigmine or edrophonium.

Pharmacokinetics:

Cisatracurium undergoes degradation in the body at physiological pH and temperature by Hofmann elimination to form laudanosine and the monoquaternary acrylate metabolite. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite. Elimination of cisatracurium is largely organ independent but the liver and kidneys are primary pathways for the clearance of its metabolites. These metabolites do not possess neuromuscular blocking activity.

Pharmacokinetics in Adult patients: The ED_{95} (dose required to produce 95% depression of the twitch response of the adductor pollicis muscle to stimulation of the ulnar nerve) of cisatracurium is estimated to be 0,05 mg/kg bodyweight during opioid anaesthesia (thiopentone/fentanyl/midazolam). The ED_{95} of cisatracurium besylate in children during halothane anaesthesia is 0,04mg/kg. Non-compartmental pharmacokinetics of cisatracurium are independent of dose in the range studied (0,1 to 0,2 mg/kg, i.e. 2 to 4 x ED_{95}). Pharmacokinetic parameters after doses of 0,1 and 0,2 mg/kg NIMBEX Injection administered to healthy adult surgical patients are summarised in the table below.

Parameter	Range of mean values
Clearance	4,7 to 5,7 ml/min/kg
Volume of distribution at steady state	121 to 161 ml/kg
Elimination half-life	22 to 29 min

Pharmacokinetics in Elderly Patients: There are no clinically important differences in the pharmacokinetics of cisatracurium in elderly and young adult patients.

Pharmacokinetics in Patients with Renal Impairment: There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage renal failure and in healthy adult patients. The recovery profile of cisatracurium is unchanged in the presence of renal failure.

Pharmacokinetics in Patients with Hepatic Impairment: There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage liver disease and in healthy adult patients. The recovery profile was unchanged.

Pharmacokinetics During Infusions: The pharmacokinetics of cisatracurium after infusions of NIMBEX Injection are similar to those after single bolus injection. The recovery profile after infusion of NIMBEX Injection is independent of duration of infusion and is similar to that after single bolus injections.

Pharmacokinetics in Intensive Care Unit (ICU) Patients: The pharmacokinetics of cisatracurium in ICU patients receiving prolonged infusions are similar to those in healthy surgical adults receiving infusions or single bolus injections. The recovery profile after infusions of NIMBEX Injection in ICU patients is independent of duration of infusion. When laudanosine was administered to experimental animals, high concentrations were associated with hypotension and, in some species, cerebral excitation. However, there is no evidence that laudanosine has caused such effects in man even after prolonged infusions of cisatracurium to ICU patients with impaired renal and/or hepatic function.

INDICATIONS

NIMBEX is used during surgical procedures to relax skeletal muscles and to facilitate controlled ventilation. NIMBEX is suitable for endotracheal intubation especially where subsequent muscle relaxation is required.

CONTRAINDICATIONS

NIMBEX Injection is contra-indicated in patients known to be hypersensitive to cisatracurium, atracurium, or benzenesulphonic acid.

Use and safety in pregnancy and lactation has not been established.

Neonates, as NIMBEX Injection has not been studied in this patient population.

WARNINGS:

CISATRACURIUM PARALYSES THE RESPIRATORY MUSCLES AS WELL AS OTHER SKELETAL MUSCLES BUT HAS NO EFFECT ON CONSCIOUSNESS OR PAIN THRESHOLD. NIMBEX INJECTION SHOULD ONLY BE ADMINISTERED BY OR UNDER THE SUPERVISION OF AN ANAESTHETIST. FACILITIES FOR TRACHEAL INTUBATION, AND MAINTENANCE OF PULMONARY VENTILATION AND ADEQUATE ARTERIAL OXYGENATION MUST BE AVAILABLE. MONITORING OF NEUROMUSCULAR FUNCTION IS RECOMMENDED DURING THE USE OF NIMBEX INJECTION IN ORDER TO INDIVIDUALISE DOSAGE REQUIREMENTS.

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

ICU Patients: When laudanosine, a metabolite of cisatracurium, was administered to experimental animals, high concentrations were associated with hypotension and, in some species, cerebral excitation.

DOSAGE AND DIRECTIONS FOR USE

Use by intravenous bolus injection:

***Dosage in adults*:**

Tracheal Intubation: The recommended intubation dose of NIMBEX Injection for adults is 0,15 mg/kg. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection. Higher doses will shorten the time to onset of neuromuscular block. The following table summarises mean pharmacodynamic data when NIMBEX Injection was

administered at doses of 0,1 to 0,4 mg/kg to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

Initial NIMBEX Injection Dose (mg/kg)	Anaesthetic Background	Time to 90% T_1[a] Suppression (min)	Time to Maximum T_1[a] Suppression (min)	Time to 25% Spontaneous T_1[a] Recovery (min)
0,1	Opioid	3,4	4,8	45
0,15	Propofol	2,6	3,5	55
0,2	Opioid	2,4	2,9	65
0,4	Opioid	1,5	1,9	91

[a] Single twitch response as well as the first component of the Train-of-Four response of the adductor pollicis muscle following supramaximal electrical stimulation of the ulnar nerve.

Maintenance: Neuromuscular block can be extended with maintenance doses of NIMBEX Injection. A dose of 0,03 mg/kg provides approximately 20 minutes of additional clinically effective neuromuscular block during opioid or propofol anaesthesia. Consecutive maintenance doses do not result in progressive prolongation of effect.

Spontaneous Recovery: Once spontaneous recovery from neuromuscular block is underway, the rate is independent of the NIMBEX dose. During opioid or propofol anaesthesia, the median times from 25 to 75% and from 5 to 95% recovery are approximately 13 and 30 minutes, respectively.
Reversal: Neuromuscular block following NIMBEX administration is reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T_4:T_1 ratio $\geq$0,7) are approximately 4 and 9 minutes respectively, following administration of the reversal agent at an average of 10% T_1 recovery.

Dosage in paediatric patients aged 1 month to 12 years:

Tracheal Intubation: As in adults, the recommended intubation dose of NIMBEX Injection is 0,15 mg/kg administered rapidly over 5 to 10 seconds. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection of NIMBEX. Pharmacodynamic data for this dose are presented in the tables below. If a shorter clinical duration is required, pharmacodynamic data suggest that a dose of 0,1 mg/kg may produce similar intubation conditions at 120 to 150 seconds.

In paediatric patients aged 1 month to 12 years, NIMBEX has a shorter clinically effective duration and a faster spontaneous recovery profile than those observed in adults under similar anaesthetic conditions. Small differences in the pharmacodynamic profile were observed between the age ranges 1 to 11 months and 1 to 12 years which are summarised in the tables below.

Paediatric Patients aged 1 to 11 months:

Initial NIMBEX Injection Dose (mg/kg)	**Anaesthetic Background**	**Time to 90% Suppression (min)**	**Time to Maximum Suppression (min)**	**Time to 25% Spontaneous T_1 Recovery (min)**
0,15	Halothane	1,4	2,0	52
0,15	Opioid	1,4	2,0	47

Paediatric Patients aged 1 to 12 years:

Initial NIMBEX Injection Dose (mg/kg)	**Anaesthetic Background**	**Time to 90% Suppression (min)**	**Time to Maximum Suppression (min)**	**Time to 25% Spontaneous T_1 Recovery (min)**
0,08	Halothane	1,7	2,5	31
0,1	Opioid	1,7	2,8	28
0,15	Halothane	2,3	3,0	43
0,15	Opioid	2,6	3,6	38

Halothane may be expected to extend the clinically effective duration of a dose of NIMBEX by up to 20%. No information is available on the use of NIMBEX in children during isoflurane anaesthesia but these agents may also be expected to extend the clinically effective duration of a dose of NIMBEX by up to 20%.

Maintenance: Neuromuscular block can be extended with maintenance doses of NIMBEX Injection. A dose of 0,02 mg/kg provides approximately 9 minutes of additional clinically effective neuromuscular block during halothane anaesthesia. Consecutive maintenance doses do not result in progressive prolongation of effect.

Spontaneous Recovery: Once recovery from neuromuscular block is underway, the rate is independent of the NIMBEX dose administered. During opioid or halothane anaesthesia, the median times from 25 to 75% and from 5 to 95% recovery are approximately 11 and 28 minutes, respectively.

Reversal: Neuromuscular block following NIMBEX administration is reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T_4:T_1 ratio ≥0,7) are approximately 2 and 5 minutes respectively, following administration of the reversal agent at an average of 13% T_1 recovery.

Use by intravenous infusion:

Dosage in adults and children aged 2 to 12 years:

Maintenance of neuromuscular block may be achieved by infusion of NIMBEX Injection.

An initial infusion rate of 3 μg/kg/min (0,18 mg/kg/hr) is recommended to restore 89 to 99% T_1 suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 to 2 μg/kg/min (0,06 to 0,12 mg/kg/hr) should be adequate to maintain block in this range in most patients.

Reduction of the infusion rate by up to 40% may be required when NIMBEX Injection is administered during isoflurane or enflurane anaesthesia (see INTERACTIONS). The infusion rate will depend upon the concentration of cisatracurium in the infusion solution, the desired degree of neuromuscular block, and the patient's weight. The following table provides guidelines for delivery of undiluted NIMBEX Injection.

Infusion Delivery Rate of NIMBEX Injection 2 mg/ml

Patient Weight (kg)	Dose (μg/kg/min) 1,0	1,5	2,0	3,0	Infusion Rate
20	0,6	0,9	1,2	1,8	ml/hr
70	2.1	3,2	4,2	6,3	ml/hr
100	3.0	4,5	6,0	9,0	ml/hr

Steady rate continuous infusion of NIMBEX Injection is not associated with a progressive increase or decrease in neuromuscular blocking effect.

Following discontinuation of infusion of NIMBEX Injection, spontaneous recovery from neuromuscular block proceeds at a rate comparable to that following administration of a single bolus.

Dosage in neonates aged less than 1 month:

No dosage recommendation for neonates can be made until further information becomes available.

Dosage in elderly patients:

No dosing alterations are required in elderly patients. In these patients NIMBEX Injection has a similar pharmacodynamic profile to that observed in young adult patients, but as with other neuromuscular blocking agents, it may have a slightly slower onset.

Dosage in patients with renal impairment:

No dosing alterations are required in patients with renal failure. In these patients, NIMBEX Injection has a similar pharmacodynamic profile to that observed in patients with normal renal function, but it may have a slightly slower onset.

Dosage in patients with hepatic impairment:

No dosing alterations are required in patients with end-stage liver disease. In these patients NIMBEX Injection has a similar pharmacodynamic profile to that observed in patients with normal hepatic function but it may have a slightly faster onset.

Dosage in patients with cardiovascular disease:

NIMBEX has been used to provide neuromuscular block in patients undergoing cardiac surgery. When administered by rapid bolus injection (over 5 to 10 seconds) to patients with serious cardiovascular disease, NIMBEX has not been associated with clinically significant cardiovascular effects in any dose studied (up to and including 0,4 mg/kg (8x ED_{95}).

Dosage in Intensive Care Unit (ICU) patients:

NIMBEX Injection may be administered by bolus dose and/or infusion to adult patients in the ICU. An initial infusion rate of NIMBEX Injection of 3 μg/kg/min (0,18 mg/kg/hr) is recommended for adult ICU patients. There may be wide interpatient variation in dosage requirements and these may increase or decrease with time. In clinical studies the average infusion rate was 3 μg/kg/min [range 0,5 to 10,2 μg/kg/min (0,03 to 0,6 mg/kg/h)]. The median time to full spontaneous recovery following long-term (up to 6 days) infusion of NIMBEX Injection in ICU patients was approximately 50 minutes.

Infusion Delivery Rate of NIMBEX Injection 5 mg/ml

Patient Weight (kg)	Dose (μg/kg/min) Infusion Rate 1,0	1,5	2,0	3,0	
70	0,8	1,2	1,7	2,5	ml/hr
100	1,2	1,8	2,4	3,6	ml/hr

The recovery profile after infusions of NIMBEX Injection to ICU patients is independent of duration of infusion.

Dosage in patients undergoing hypothermic cardiac surgery:

There have been no studies of NIMBEX Injection in patients undergoing surgery with induced hypothermia (25 to 28 °C). The rate of infusion required to maintain adequate surgical relaxation under these conditions may be expected to be significantly reduced.

Dilution:

Diluted NIMBEX Injection is physically and chemically stable for at least 12 hours at 5 °C and 25 °C at concentrations between 0,1 and 2,0 mg/ml in the following infusion fluids, in either polyvinyl chloride (PVC) or or polypropylene containers:-

Sodium Chloride (0,9% w/v) Intravenous Infusion, Glucose (5% w/v) Intravenous Infusion, Sodium Chloride (0,18% w/v) and Glucose (4% w/v) Intravenous Infusion, Sodium Chloride (0,45% w/v) and Glucose (2,5% w/v) Intravenous Infusion.

However, since the product contains no antimicrobial preservative dilution should be carried out immediately prior to use, administration should commence as soon as possible thereafter and any remaining solution should be discarded.

NIMBEX Injection is not chemically stable when diluted with Lactated Ringer's Injection.

NIMBEX Injection has been shown to be compatible with the following commonly used peri-operative drugs, when mixed in conditions simulating administration into a running intravenous infusion via a Y-site injection port:alfentanil hydrochloride, droperidol, fentanyl citrate, midazolam hydrochloride and sufentanil citrate. Where other drugs are administered through the same indwelling needle or cannula as NIMBEX Injection, it is recommended that each drug be flushed through with an adequate volume of a suitable intravenous fluid, e.g. Sodium Chloride Intravenous Infusion 0,9% (w/v).

Since NIMBEX Injection is stable only in acidic solutions it should not be mixed in the same syringe or administered simultaneously through the same needle with alkaline solutions, e.g. sodium thiopentone. It is not compatible with ketorolac, trometamol or propofol injectable emulsion.

When a small vein is selected as the injection site, NIMBEX Injection should be flushed through the vein with a suitable intravenous fluid, e.g. Sodium Chloride Intravenous Infusion (0,9% w/v).

SIDE EFFECTS AND SPECIAL PRECAUTIONS

No adverse experiences occurred during the clinical development programme that were considered to be reasonably attributable to NIMBEX Injection. Adverse experiences, considered possibly attributable, occurred with a frequency of less than 0,5%. These were cutaneous flushing or rash, bradycardia, hypotension and bronchospasm.

Severe anaphylactic reactions have been reported in patients receiving NIMBEX in conjunction with one or more anaesthetics.

There have been some reports of persistent muscle weakness and/or myopathy following prolonged use of NIMBEX in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids.

Precautions:

Great caution should be exercised when administering NIMBEX Injection to patients who have shown allergic hypersensitivity to other neuromuscular blocking agents since cross-reactivity between neuromuscular blocking agents has been reported.

Cisatracurium does not have significant vagolytic or ganglion-blocking properties. Consequently, NIMBEX Injection has no clinically significant effect on heart rate and will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery.

Patients with myasthenia gravis and other forms of neuromuscular disease have shown greatly increased sensitivity to non-depolarising blocking agents. An initial dose of not more than 0,02 mg/kg NIMBEX Injection is recommended in these patients.

Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking agents.

NIMBEX Injection has not been studied in patients with a history of malignant hyperthermia. Studies in malignant hyperthermia-susceptible pigs indicated that cisatracurium does not trigger this syndrome.

Cisatracurium has not been studied in patients with burns; however, as with other non-depolarising neuromuscular blocking agents, the possibility of increased dosing requirements and shortened duration of action must be considered if NIMBEX Injection is administered to these patients.

Interactions:

Many drugs have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents, including the following:

Increased effect:

Anaesthetics: Volatile agents such as enflurane, isoflurane and halothane;

Ketamine;

Other non-depolarising neuromuscular blocking agents;

Other drugs:

Antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin;

Anti-arrhythmic drugs, including propranolol, calcium channel blockers, lignocaine, procainamide and quinidine;

Diuretics, including furosemide and possibly thiazides, mannitol and acetazolamide;

Magnesium salts;

Lithium salts;

Ganglion blocking drugs: trimetaphan, hexamethonium.

Decreased effect:

Prior chronic administration of phenytoin or carbamazepine;

Prior administration of suxamethonium has no effect on the duration of neuromuscular block following bolus doses of NIMBEX Injection or on infusion rate requirements;

Administration of suxamethonium to prolong the effects of non-depolarising neuromuscular blocking agents may result in a prolonged and complex block which can be difficult to reverse with anticholinesterases;

Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to non-depolarising neuromuscular blocking agents might result. 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage with NIMBEX Injection.

It is essential to maintain pulmonary ventilation and arterial oxygenation until adequate spontaneous respiration returns. Full sedation will be required since consciousness is not impaired by NIMBEX Injection. Recovery may be accelerated by the administration of anticholinesterase agents once evidence of spontaneous recovery is present.

IDENTIFICATION

A clear, pale yellow or greenish yellow solution, free from visible particulate matter.

PRESENTATION:

NIMBEX 2 mg/ml (2,5 ml) Injection: Box of 5 ampoules

NIMBEX 2 mg/ml (5 ml) Injection: Box of 5 ampoules

NIMBEX 2 mg/ml (10 ml) Injection: Box of 5 ampoules

NIMBEX 5: Box with one 30 ml vial

STORAGE INSTRUCTIONS

Unopened ampoule/vial:

Keep out of reach of children.

Store between 2 and 8 °C.

Do not freeze.

Protect from light.

In addition, the diluted solution can be stored at 5 or 25 °C.

This product is marketed as a single dose ampoule/vial and any unused portion of the solution must be discarded.

The ampoule/vial must not be removed from the outer carton until such time as it is required for administration.

REGISTRATION NUMBER

NIMBEX 2 mg/ml (2,5 ml) Injection: 31/17.1/0255

NIMBEX 2 mg/ml (5 ml) Injection: 31/17.1/0444

NIMBEX 2 mg/ml (10 ml) Injection: 31/17.1/0445

NIMBEX 5 Injection: 31/17.1/0256

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

Pharmacare Limited

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF PACKAGE INSERT

27 November 1998

NAMIBIA

Nimbex 2 mg/ml (2,5 ml): NS2 04/17.1/0929
Nimbex 2 mg/ml (5 ml): NS2 04/17.1/0928
Nimbex 2 mg/ml (10 ml): NS2 04/17.1/0927
Nimbex 5: NS2 04/17.1/0935

BOTSWANA

Nimbex 2 mg/ml (2,5 ml): S2 BOT1502681
Nimbex 2 mg/ml (5 ml): S2 BOT1502681A
Nimbex 2 mg/ml (10 ml): S2 BOT1502681B
Nimbex 2 mg/ml (2,5 ml): PP 2014/1.3/4915
Nimbex 2 mg/ml (5 ml): PP 2014/1.3/4916
Nimbex 2 mg/ml (10 ml): PP 2014/1.3/4917

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