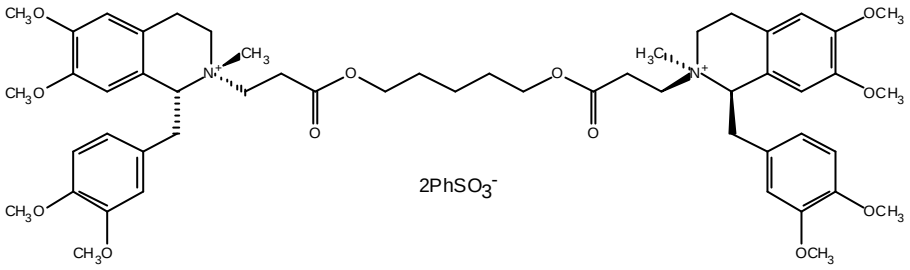
PRODUCT INFORMATION

NIMBEX® Injection

NAME OF THE DRUG:

Cisatracurium besylate

The chemical name of cisatracurium besylate is (1R,1'R,2R,2'R,)-2,2'-(3,11-dioxo-4,10-dioxatridecamethylene) bis (1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate. The molecular formula of cisatracurium besylate is $C_{65}H_{82}N_2O_{18}S_2$ and it has a molecular weight of 1243.5. The structural formula is given below:



CAS Number: 96946-42-8

DESCRIPTION:

Cisatracurium besylate is a white to pale yellow powder.

Nimbex Injection is supplied in two strengths, either 2 mg or 5 mg of cisatracurium besylate per mL. Nimbex Injection also contains Water for Injections and benzenesulfonic acid. Nimbex Injection does not contain any preservative and is intended for single patient use only.

PHARMACOLOGY:

Pharmacodynamics

Cisatracurium besylate, a stereoisomer of atracurium, is an intermediate duration, non-depolarising benzylisoquinolinium skeletal muscle relaxant. Cisatracurium besylate 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.

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 besylate is estimated to be 0.05 mg/kg bodyweight during opioid anaesthesia (thiopentone, fentanyl, midazolam). The recommended intubation dose for cisatracurium in adults is 3 x ED_{95}, which has a longer clinically effective duration than the recommended intubation dose of atracurium (2 x ED_{95}) (see **DOSAGE AND ADMINISTRATION**).

The ED_{95} of cisatracurium besylate in children during halothane anaesthesia is 0.04 mg/kg bodyweight.

Cisatracurium besylate 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 besylate 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
Non-compartmental pharmacokinetics of cisatracurium besylate are independent of dose in the range studied (0.1 to 0.2 mg/kg bodyweight; ie. 2 to 4 x ED_{95}). Population pharmacokinetic modelling confirms and extends these findings up to 0.4 mg/kg bodyweight (8 x ED_{95}). Pharmacokinetic parameters after doses of 0.1 and 0.2 mg/kg bodyweight Nimbex Injection administered to healthy adult surgical patients are summarised 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 during infusions
The pharmacokinetics of cisatracurium besylate following infusion of Nimbex Injection are similar to those following a single bolus injection. Pharmacokinetics were studied in healthy adult surgical patients who received an initial 0.1 mg/kg bolus dose of Nimbex Injection followed by a maintenance infusion of Nimbex Injection to maintain 89 to 99% T_1 suppression. Mean clearance of cisatracurium besylate was 6.9 mL/kg/min and the elimination half-life was 28 minutes. During infusion of cisatracurium besylate peak plasma concentrations of laudanosine and the monoquaternary alcohol metabolites are approximately 6% and 11% of the parent compound, respectively.

The recovery profile after infusion of Nimbex Injection is independent of the duration of infusion and is similar to that after single bolus injection.

Pharmacokinetics in Intensive Care Unit (ICU) patients
The pharmacokinetics of cisatracurium besylate in ICU patients receiving prolonged infusion are similar to those in healthy surgical adults receiving infusion or single bolus injection. Mean clearance of cisatracurium besylate was 7.5 mL/kg/min and the elimination half-life was 27 minutes. The recovery profile after infusions of Nimbex Injection in ICU patients is independent of duration of infusion.

Concentrations of metabolites are higher in ICU patients with abnormal renal and/or hepatic functions (see **PRECAUTIONS**). These metabolites do not contribute to neuromuscular block.

Pharmacokinetics in elderly patients
There are no clinically important differences in the pharmacokinetics of cisatracurium besylate in elderly patients. In a comparative study plasma clearance was unaffected by age. Minor differences in volume of distribution (+17%) and half-life (+4 min) did not affect the recovery profile.

Pharmacokinetics in paediatric patients
No full study has been performed to assess the pharmacokinetics of cisatracurium in paediatric patients.

The population pharmacokinetics/pharmacodynamics of cisatracurium were described in 20 healthy paediatric patients during halothane anaesthesia, using the same model developed for healthy adult patients. The clearance was higher in healthy paediatric patients (5.89 mL/min/kg) than in healthy adult patients (4.57 mL/min/kg) during opioid anaesthesia. The rate of equilibration between plasma concentrations and neuromuscular block, as indicated by k_{e0}, was faster in healthy paediatric patients receiving halothane anaesthesia (0.1330 minutes^{-1}) than in healthy adult patients receiving opioid anaesthesia (0.0575 minutes^{-1}). The EC_{50} in healthy paediatric patients (125 ng/mL) was similar to the value in healthy adult patients (141 ng/mL) during opioid anaesthesia. The minor differences in the pharmacokinetic/pharmacodynamic parameters of cisatracurium were associated with a faster time to onset and a shorter duration of cisatracurium-induced neuromuscular block in paediatric patients.

Pharmacokinetics in patients with renal impairment
There are no clinically important differences in the pharmacokinetics of cisatracurium besylate in patients with end-stage renal failure. In a comparative study there were no statistically significant or clinically important differences in pharmacokinetic parameters of cisatracurium besylate. The recovery profile of cisatracurium besylate 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 besylate in patients with end-stage liver disease. In a comparative study of patients undergoing liver transplantation and healthy adults there were small differences in volume of distribution (+21%) and clearance (+16%). There were no differences in the elimination half-life of cisatracurium besylate. The recovery profile was unchanged.

CLINICAL TRIALS:

The cisatracurium clinical development programme was constructed to provide for systematic collection of efficacy and safety data and to ensure exposure to therapeutically relevant doses of cisatracurium in various populations of patients undergoing a diversity of surgical procedures during opioid, propofol or inhalation anaesthesia as well as ICU patients who require neuromuscular blocking agents to facilitate mechanical ventilation. The result was 23 clinical trials conducted in 1295 surgical and ICU patients administered cisatracurium and 255 patients administered control neuromuscular blocking agents (atracurium or vecuronium). A total of 20 of these studies contributed efficacy data and included 1206 patients administered cisatracurium. All studies contributed safety data.

The major populations of patients were classified by the American Society of Anesthesiologists (ASA) Classification or New York Heart Association (NYHA) Classification as:

- Healthy (ASA Class 1 or 2) young adult (aged 18-50 years), elderly adult (aged 65-89) and paediatric patients (aged 1 month-12 years).
- Seriously ill (ASA Class 3 or 4) elderly patients or patients with end-stage renal or hepatic disease.
- Seriously ill (NYHA Class I to IV) adult patients with serious cardiovascular disease scheduled for Coronary Artery Bypass Graft (CABG) surgery.
- Critically ill adult ICU patients requiring neuromuscular blocking agents to facilitate mechanical ventilation.

The studies included 660 healthy adult patients, 236 paediatric patients (aged 2-12 years), 110 paediatric patients (aged 1-23 months), 15 patients with end-stage liver disease (ESLD), 17 patients with end-stage renal failure (ESRF), 182 patients with serious cardiovascular disease (undergoing coronary artery bypass graft surgery) and 68 critically ill patients in the ICU. Forty-eight elderly patients (≥ 65 years) were specifically studied in two studies. Overall, 172 (13%) of the patients administered cisatracurium were ≥ 65 years.

The most common types of surgical procedures were urological (28% of cisatracurium patients) and CABG (14% of cisatracurium patients). Other types of procedures included general surgery (11%), gynaecological (7%), neurosurgical (5%), orthopaedic (8%), oral (3%), plastic (2%), ear, nose and throat (3%) and vascular (1%). ICU patients accounted for 5% of patients administered cisatracurium. There were no obstetric studies.

The clinical development programme acquired substantive data in regard to efficacy and safety of large bolus doses of cisatracurium. The mean clinically effective dose of cisatracurium (ED_{95}) estimated from two dose-response studies of adult patients receiving opioid anaesthesia was 0.05 mg/kg. Of the 1295 patients to whom cisatracurium was administered in clinical trials, 102 (8%) received initial bolus doses < ED_{95}, 649 (50%) received initial bolus doses in the ED_{95} to $2 \times ED_{95}$ range, and 515 (40%) received initial doses that exceeded $2 \times ED_{95}$. ICU patients had neuromuscular block initiated with an infusion and/or bolus dose.

Following the initial dose of cisatracurium, many patients received one or more additional bolus doses, continuous intravenous (iv) infusion, or both to maintain an adequate level of neuromuscular block. The use of cisatracurium by continuous infusion during surgical procedures requiring extended neuromuscular block was investigated in healthy (ASA Class 1 or 2) adult patients in 7 studies. The majority of patients received cisatracurium by infusion during opioid anaesthesia, the duration of infusion ranging from 11-261 minutes. Maintenance dose data for cisatracurium were captured in 6 studies, a total of 154 adult surgical patients being administered 1-21 maintenance doses of 0.03 mg/kg.

The adequacy of intubation conditions following cisatracurium was assessed in 5 studies in a total of 480 patients (aged 1 month to 87 years) administered cisatracurium.

INDICATIONS:

Nimbex Injection is indicated for use during surgical and other procedures and in intensive care to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation. It is used as an adjunct to general anaesthesia, or sedation in the intensive care unit.

CONTRAINDICATIONS:

Nimbex Injection is contraindicated in patients known to be hypersensitive to cisatracurium besylate, atracurium or benzenesulfonic acid.

PRECAUTIONS:

Cisatracurium besylate 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, anaesthetists or other clinicians who are familiar with the use and action of neuromuscular blocking agents. Facilities for tracheal intubation and maintenance of pulmonary ventilation and adequate arterial oxygenation should be available.

Little information is available on the plasma levels and clinical consequences of cisatracurium metabolites that may accumulate during days to weeks of cisatracurium administration in ICU patients. Laudanosine, a major biologically active metabolite of atracurium and cisatracurium 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. Consistent with the decreased infusion rate requirements of cisatracurium, plasma laudanosine concentrations are approximately one third those following atracurium infusion. There have been rare spontaneous reports of seizures in ICU patients who have received atracurium and other agents. These patients usually had predisposing causes (such as cranial trauma, cerebral oedema, hypoxic encephalopathy, viral encephalitis, uraemia). There are insufficient data to determine whether or not laudanosine contributes to seizures in ICU patients.

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 agents has been reported.

Cisatracurium besylate 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 bodyweight cisatracurium besylate is recommended in these patients.

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 (**see DRUG INTERACTIONS**).

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

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

Patients with burns have been shown to develop resistance to non-depolarising neuromuscular blocking agents, including atracurium. The extent of altered response depends upon the size of the burn and the time elapsed since the burn injury. Nimbex has not been studied in patients with burns, however, based on its structural similarity to atracurium, the

possibility of increased dosing requirements and shortened duration of action must be considered if Nimbex is administered to burn patients.

As with other neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of Nimbex Injection in order to individualise dosage requirements.

As with other drugs administered intravenously, when a small vein is selected as the injection site, Nimbex Injection should be flushed through the vein with a suitable intravenous fluid (eg. Sodium Chloride Intravenous Solution 0.9% w/v).

Nimbex Injection does not contain an antimicrobial preservative. Dilution should, therefore, be carried out immediately prior to use. Administration should commence as soon as possible thereafter and any remaining solution should be discarded (**see Instructions for use**).

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

Enflurane or isoflurane anaesthesia may extend the clinically effective duration of an initial dose of Nimbex by as much as 15% in adults. In children, 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 or enflurane anaesthesia but these agents may also be expected to extend the clinically effective duration of a dose of Nimbex by up to 20%.

Mutagenicity / Carcinogenicity
Carcinogenesis and fertility studies have not been performed. Cisatracurium was evaluated for genotoxic potential in a battery of four tests. It was non-genotoxic in assays for clastogenic activity (*in vitro* human lymphocyte cytogenetics assay and a rat bone marrow cytogenetics assay) and an Ames Salmonella assay for gene mutations. As was the case with atracurium, the mouse lymphoma assay was positive.

Use in Pregnancy
Pregnancy Category: C
Teratology studies in non-ventilated pregnant rats treated subcutaneously with maximum subparalysing doses (4 mg/kg daily) and in ventilated rats treated intravenously with paralysing doses of cisatracurium (1.0 mg/kg), respectively, revealed no fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of cisatracurium in pregnant women. Because animal studies are not always predictive of human response, cisatracurium should be used during pregnancy only if clearly needed.

Doses of 0.2 or 04 mg/kg cisatracurium given to female beagles undergoing caesarean section resulted in negligible levels of cisatracurium in umbilical vessel blood of neonates and no deleterious effects on the puppies.

Use in lactation
Studies have not been conducted to determine whether cisatracurium or its metabolites are excreted in human or animal milk.

Effects on laboratory tests
None known.

DRUG INTERACTIONS:

A number of drugs have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents.

The following drugs have been shown to increase the effects of non-depolarising neuromuscular blocking agents.

Anaesthetics:
Volatile anaesthetics such as enflurane, isoflurane and halothane (see **PRECAUTIONS).**
Ketamine.
Other non-depolarising neuromuscular blocking agents.
Antibiotics, including:
the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin.
Anti-arrhythmic drugs, including:
propanolol, calcium channel blockers, lignocaine, procainamide and quinidine.
Diuretics, including:
frusemide and possibly thiazides, mannitol and acetazolamide.
Magnesium salts.
Lithium salts.
Ganglion blocking drugs (trimetaphan, hexamethonium).

Prior chronic administration of phenytoin or carbamazepine has been shown to decrease the effects of non-depolarising neuromuscular blocking agents.

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 (propanolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), anti-rheumatic drugs (chloroquine, penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

ADVERSE REACTIONS:

Observed in clinical trials of surgical patients

No adverse experiences considered to be reasonably attributable to Nimbex Injection were reported amongst 937 surgical patients studied during the clinical development programme. The following adverse experiences were judged by investigators during the clinical trials to have a possible causal relationship to administration of Nimbex:

Incidence Greater than 1%: None.

Incidence Less than 1%:

Cardiovascular: Bradycardia (0.4%), hypotension (0.2%), flushing (0.2%).

Respiratory: Bronchospasm (0.2%).

Dermatological: Rash (0.1%).

Observed in clinical trials of intensive care unit patients

Three adverse experiences were reported among 68 ICU patients administered Nimbex Injection in conjunction with other drugs in clinical studies. One patient experienced bronchospasm, considered possibly attributable to Nimbex Injection. In one of the two ICU studies, a randomised and double-blind study of ICU patients using TOF neuromuscular monitoring, there were two reports of prolonged recovery (167 and 270 minutes) among 28 patients administered Nimbex and 13 reports of prolonged recovery (range: 90 minutes to 33 hours) among 30 patients administered vecuronium.

Observed During Clinical Practice

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of cisatracurium besylate in conjunction with one or more anaesthetic agents in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to cisatracurium besylate.

Hypersensitivity

Very rarely: Severe anaphylactic reactions have been reported in patients receiving Nimbex in conjunction with one or more anaesthetic agents.

Anaphylactic reactions of varying degrees of severity have been observed after the administration of neuromuscular blocking agents.

Other reported reactions

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

DOSAGE AND ADMINISTRATION:

Nimbex Injection contains no antimicrobial preservative and is intended for single patient 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 bodyweight. 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 bodyweight to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

Initial Nimbex Injection Dose (mg/kg bodyweight)	Anaesthetic Background	Time to 90% T_1® Suppression (min)	Time to Maximum T_1® Suppression (min)	Time to Spontaneous T_1® 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

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

Enflurane or isoflurane anaesthesia may extend the clinically effective duration of an initial dose of Nimbex by as much as 15%.

Maintenance. Neuromuscular block can be extended with maintenance doses of Nimbex Injection. A dose of 0.03 mg/kg bodyweight 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 administered dose of Nimbex Injection. 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 the administration of Nimbex Injection is readily reversible with standard doses of anticholinesterase agents. Following the administration of the reversal agent at an average of 10% T_1 recovery, 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.

Dosage in Paediatric Patients ages 1 month to 12 years

Tracheal Intubation. As in adults, the recommended intubation dose of Nimbex Injection is 0.15 mg/kg bodyweight 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 bodyweight 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 with 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. Younger children (1 – 11 months old) demonstrated a longer mean clinical effective duration, as compared to the older children. However, there was no significant difference in the mean 25-75% recovery indices between the age groups.

Paediatric Patients aged 1 to 11 months

Initial Nimbex Injection Dose (mg/kg	Number of patients studied	Anaesthetic Background	Time to 90% Suppression (min)	Time to Maximum Suppression	Time to 25% Spontaneous T_1 Recovery

bodyweight)				(min)	(min)
0.15	30	Halothane	1.4	2.0	52
0.15	30	Opioid	1.4	1.9	47

Paediatric Patients aged 1 to 12 years

Initial Nimbex Injection Dose (mg/kg bodyweight)	Number of patients studied	Anaesthetic Background	Time to 90% Suppression (min)	Time to Maximum Suppression (min)	Time to 25% Spontaneous T_1 Recovery (min)
0.15	60	Halothane	2.3	3.0	43
0.15	59	Opioid	2.6	3.6	38

Data in the above tables are derived from Study 139-027, an open-label study in ASA I/II paediatric patients aged 1 month to 12 years. For data presented, patients were randomised to N_2O/O_2/ halothane (n=**90**) or N_2O/O_2/opioid (n=**89**) anaesthesia. Within each anaesthetic group patients were stratified into three age groups; 1-11 months, 12-59 months or 60-155 months. Neuromuscular blocking profile was assessed at the adductor pollicis by electromyography.

When Nimbex is not required for intubation: a dose of less than 0.15mg/kg can be used. Pharmacodynamic data for doses of 0.08 and 0.1mg/kg for paediatric patients aged 2 to 12 years are presented in the table below:

Initial Nimbex Injection Dose (mg/kg bodyweight)	Number of patients studied	Anaesthetic Background	Time to 90% Suppression (min)	Time to Maximum Suppression (min)	Time to 25% Spontaneous T_1 Recovery (min)
0.08	32	Halothane	1.7	2.5	31
0.1	16	Opioid	1.7	2.8	28

Data in the above table are derived from Study 139-011, an open-label study in ASA I/II paediatric patients aged 2-12 years. Neuromuscular block was assessed at the adductor pollicis by electromyography.

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 or enflurane 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 bodyweight 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. During opioid anaesthesia the median times from 25 to 75% and from 5 to 95% recovery are approximately 10 and 25 minutes respectively.

Reversal. Neuromuscular block following the administration of Nimbex Injection is readily reversible with standard doses of anticholinesterase agents. Following the administration of the reversal agent at an average of 13% T_1 recovery, 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.

Use by intravenous infusion

Dosage in Adults and Paediatric Patients aged 1 month 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 DRUG INTERACTIONS**).

The infusion rate will depend upon the concentration of cisatracurium besylate in the infusion solution, the desired degree of neuromuscular block and the patient's weight. The following table provides guidance for delivery of undiluted Nimbex Injection 2 mg/mL.

Infusion Delivery Rate of Nimbex Injection 2 mg/mL

Patient Weight (kg)	Dose (µg/kg/min)				Infusion Rate
	1.0	1.5	2.0	3.0	
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

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 injection.

Dosage in neonates aged less than 1 month
No dosage recommendation for neonates can be made as administration of Nimbex Injection has not been studied in this patient population.

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 or 0.03 to 0.6 mg/kg/hr).

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 infusion of Nimbex Injection to ICU patients is independent of the duration of infusion.

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, however, 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.

Patients with cardiovascular disease
Nimbex Injection has been used effectively 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 at any dose studied (up to and including 0.4 mg/kg (8 x ED_{95})).

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). As with other neuromuscular blocking agents, the rate of infusion required to maintain adequate surgical relaxation under these conditions may be expected to be significantly reduced.

Monitoring
As with other neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of Nimbex Injection in order to individualise dosage requirements.

Instructions for use

Physical Compatibilities
Diluted Nimbex Injection is chemically and physically stable for at least 12 hours, when stored in either polyvinyl chloride or polypropylene containers, at concentrations between 0.1 and 2.0 mg/mL in the following infusion solutions:

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

The product contains no antimicrobial preservative and therefore should be used immediately on dilution, or failing this should be stored at 2 to 8°C for no more than 24 hours, after which time unused solution should be discarded. Dilution should, therefore, be carried out immediately prior to use. Administration should commence as soon as possible thereafter and any remaining solution should be discarded. Containers of Nimbex Injection and any syringe containing Nimbex Injection are for single use in individual patients. At the end of the procedure or at 24 hours following preparation, whichever is the sooner, both the reservoir of Nimbex Injection and the infusion line must be discarded and replaced as appropriate.

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

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 (eg. Sodium Chloride Intravenous Infusion 0.9% w/v).

Physical Incompatibilities
Nimbex Injection is not chemically stable when diluted in Lactated Ringer's Injection.

Since Nimbex 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 (eg. thiopentone). Nimbex Injection is not compatible with ketorolac, trometamol or propofol injection emulsion.

OVERDOSAGE:

Symptoms and signs
Prolonged muscle paralysis and its consequences are expected to be the main signs of overdose with Nimbex Injection.

Management
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.

PRESENTATION:

Nimbex Injection is a colourless to pale yellow or greenish solution. It is available in strengths of either 2 mg/mL (ampoules) or 5 mg/mL (vials) in the following pack sizes:

Nimbex Injection 2 mg/mL:	5 x 2.5 mL ampoules
	5 x 5 mL ampoules
Nimbex Injection 5 mg/mL:	1 x 30 mL vial

Storage
Nimbex Injection should be stored between 2° and 8°C and protected from light.

Supplied By
GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

Date of TGA approval: 21 July 1999

Date of Amendment 3 June 2002

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

Issue No. 5