

## Cisatracurium

### QUALITATIVE AND QUANTITATIVE COMPOSITION

#### Ampoules:

A sterile solution containing 2 mg cisatracurium (bis-cation) per ml, as cisatracurium besylate, without an antimicrobial preservative, supplied in an ampoule.

#### Vials:

A sterile solution containing 5 mg cisatracurium (bis-cation) per ml, as cisatracurium besylate, without an antimicrobial preservative, supplied in a vial.

### PHARMACEUTICAL FORM

Solution for injection or infusion.

### CLINICAL PARTICULARS

#### Indications

*NIMBEX* is an intermediate-duration, non-depolarising neuromuscular blocking agent for i.v. administration. *NIMBEX* is indicated for use during surgical procedures including cardiac surgery, other procedures and in intensive care. It is used as an adjunct to general anaesthesia, or sedation in the Intensive Care Unit (ICU), to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation.

*NIMBEX* contains no antimicrobial preservative and is intended for single patient use.

#### Dosage and Administration

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

##### • Use by I.V. bolus injection in adults

**Tracheal intubation:** The recommended intubation dose of *NIMBEX* for adults 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.

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 <i>NIMBEX</i> injection dose (mg/kg) | Anaesthetic background | Time to 90% T <sub>1</sub> a suppression (min) | Time to maximum T <sub>1</sub> a suppression (min) | Time to 25% spontaneous T <sub>1</sub> 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  |

<sup>a</sup> 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.

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*. A dose of 0.03 mg/kg provides approximately 20 min 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 administered. During opioid or propofol anaesthesia, the median times from 25 to 75% and from 5 to 95% recovery are approximately 13 and 30 min, respectively.

**Reversal:** Neuromuscular block following *NIMBEX* administration is readily reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T<sub>4</sub>:T<sub>1</sub> ratio more than 0.7) are approximately 2 and 5 min, respectively, following administration of the reversal agent at an average of 13% T<sub>1</sub> recovery.

##### • Use by I.V. bolus injection in children (1 month to 12 years of age)

**Tracheal intubation:** As in adults, the recommended initial intubation dose of *NIMBEX* 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 <i>NIMBEX</i> injection dose (mg/kg) | Anaesthetic background | Time to 90% suppression (min) | Time to maximum suppression (min) | Time to 25% spontaneous T <sub>1</sub> 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 <i>NIMBEX</i> injection Dose (mg/kg) | Anaesthetic background | Time to 90% suppression (min) | Time to maximum suppression (min) | Time to 25% spontaneous T <sub>1</sub> 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 *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 provides approximately 9 min 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 min, respectively.

**Reversal:** Neuromuscular block following *NIMBEX* administration is readily reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T<sub>4</sub>:T<sub>1</sub> ratio more than or equal to 0.7) are approximately 2 and 5 min, respectively, following administration of the reversal agent at an average of 13% T<sub>1</sub> recovery.

##### • Use by I.V. infusion in adults and Children (1 month to 12 years of age)

Maintenance of neuromuscular block may be achieved by infusion of

*NIMBEX*. An initial infusion rate of 3 micrograms/kg/min (0.18 mg/kg/h) is recommended to restore 89 to 99% T<sub>1</sub> suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 to 2 micrograms/kg/min (0.06 to 0.12 mg/kg/h) 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* is administered during isoflurane or enflurane anaesthesia. (see *Interactions*).

The infusion rate will depend upon the concentration of *NIMBEX* 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*.

#### Infusion Delivery Rate of *NIMBEX* 2 mg/ml

| Patient weight (kg) | Dose (micrograms/kg/min) |     |     |     | Infusion rate |
|---------------------|--------------------------|-----|-----|-----|---------------|
|                     | 1.0                      | 1.5 | 2.0 | 3.0 |               |
| 20                  | 0.6                      | 0.9 | 1.2 | 1.8 | ml/h          |
| 70                  | 2.1                      | 3.2 | 4.2 | 6.3 | ml/h          |
| 100                 | 3.0                      | 4.5 | 6.0 | 9.0 | ml/h          |

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

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

Although not specifically studied in paediatric patients under 2 years of age, extrapolation of pharmacodynamic data for bolus doses suggests that *NIMBEX* infusion rates should be similar.

##### • Neonates aged less than 1 month

No dosage recommendation for neonates can be made as administration of *NIMBEX* has not been studied in this patient population.

##### • Elderly

No dosing alterations are required in elderly patients. In these patients *NIMBEX* 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.

##### • Patients with renal impairment

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

##### • Patients with hepatic impairment

No dosing alterations are required in patients with end-stage liver disease. In these patients *NIMBEX* 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* 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<sub>95</sub>)).

##### • ICU patients

*NIMBEX* may be administered by bolus dose and/or infusion to adult patients in the ICU.

An initial infusion rate of *NIMBEX* of 3 micrograms/kg/min (0.18 mg/kg/h) is recommended for adult ICU patients. There may be wide inter-patient variation in dosage requirements and these may increase or decrease with time. In clinical studies the average infusion rate was 3 micrograms/kg/min [range 0.5 to 10.2 micrograms/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* in ICU patients was approximately 50 min.

#### Infusion Delivery Rate of *Nimbex* Injection 5 mg/ml

| Patient weight (kg) | Dose (micrograms/kg/min) |     |     |     | Infusion rate |
|---------------------|--------------------------|-----|-----|-----|---------------|
|                     | 1.0                      | 1.5 | 2.0 | 3.0 |               |
| 70                  | 0.8                      | 1.2 | 1.7 | 2.5 | ml/h          |
| 100                 | 1.2                      | 1.8 | 2.4 | 3.6 | ml/h          |

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

##### • Patients undergoing hypothermic cardiac surgery

There have been no studies of *NIMBEX* in patients undergoing surgery with induced hypothermia (25°C 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.

### Contraindications

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

### Warnings and Precautions

*NIMBEX* paralyses the respiratory muscles as well as other skeletal muscles but has no known effect on consciousness or pain threshold. *NIMBEX* should be only 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.

Caution should be exercised when administering cisatracurium to patients who have shown hypersensitivity to other neuromuscular blocking agents since a high rate of cross-sensitivity (greater than 50%) between neuromuscular blocking agents has been reported (see Contraindications).

*NIMBEX* does not have significant vagolytic or ganglion-blocking properties. Consequently, *NIMBEX* 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* 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* has not been studied in patients with a history of malignant hyperthermia. Studies in malignant hyperthermia-susceptible pigs indicated that *NIMBEX* does not trigger this syndrome.

*NIMBEX* 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* is administered to these patients.

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

##### • ICU patients

When administered to laboratory animals in high doses, laudanosine, a metabolite of cisatracurium and atracurium, has been associated with transient hypotension and, in some species, cerebral excitatory effects.

Consistent with the decreased infusion rate requirements of *NIMBEX*, plasma laudanosine concentrations are approximately one third those following atracurium infusion.

There have been rare reports of seizures in ICU patients who have received atracurium and other agents. These patients usually had one or more medical conditions predisposing to seizures (e.g. cranial trauma, hypoxic encephalopathy, cerebral oedema, viral encephalitis, uremia). A causal relationship to laudanosine has not been established.

### 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 frusemide 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* 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.

- Treatment with anticholinesterases, commonly used in the treatment of Alzheimer's disease e.g. donepezil, may shorten the duration and diminish the magnitude of neuromuscular blockade with cisatracurium.

#### Pregnancy and Lactation

Fertility studies have not been performed.

*NIMBEX* should be used during pregnancy only if the expected benefit to the mother outweighs any potential risk to the foetus.

Animal studies have indicated that cisatracurium has no adverse effects on foetal development.

It is not known whether cisatracurium or its metabolites are excreted in human milk.

#### Effects on Ability to Drive and Use Machines

This precaution is not relevant to the use of *NIMBEX*. *NIMBEX* will always be used in combination with a general anaesthetic and therefore the usual precautions relating to performance of tasks following general anaesthesia apply.

#### Adverse Reactions

Data from pooled internal clinical trials were used to determine the frequency of very common to uncommon adverse reactions.

The following convention has been used for the classification of frequency:- very common  $\geq 1/10$ , common  $\geq 1/100$  and  $<1/10$ , uncommon  $\geq 1/1000$  and  $<1/100$ , rare  $\geq 1/10,000$  and  $<1/1000$ , very rare  $< 1/10,000$ .

#### Clinical Trial Data

##### Cardiac disorders

Common Bradycardia

##### Vascular disorders

Common Hypotension

Uncommon Cutaneous flushing

##### Respiratory, thoracic and mediastinal disorders

Uncommon Bronchospasm

##### Skin and subcutaneous tissue disorders

Uncommon Rash

##### Postmarketing Data

##### Immune system disorders

Very rare Anaphylactic reaction

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

Very rarely, severe anaphylactic reactions have been reported in patients receiving *NIMBEX* in conjunction with one or more anaesthetic agents.

##### Musculoskeletal and connective tissue disorders

Very rare Myopathy, muscle weakness

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

These events have been reported infrequently in association with *NIMBEX* and a causal relationship has not been established.

#### Overdose

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

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*. Recovery may be accelerated by the administration of anticholinesterase agents once evidence of spontaneous recovery is present.

#### PHARMACOLOGICAL PROPERTIES

##### Pharmacodynamics

Cisatracurium is an intermediate-duration, non-depolarising benzylisoquinolinium skeletal muscle relaxant.

Clinical studies in man indicated that *NIMBEX* is not associated with dose-dependent histamine release even at doses up to and including  $8 \times ED_{95}$ .

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.

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 *NIMBEX* in children during halothane anaesthesia is 0.04 mg/kg.

##### Pharmacokinetics

Non-compartmental pharmacokinetics of *NIMBEX* are independent of dose in the range studied (0.1 to 0.2 mg/kg, i.e. 2 to 4 x  $ED_{95}$ ).

Population pharmacokinetic modelling confirms and extends these findings up to 0.4 mg/kg ( $8 \times ED_{95}$ )

##### Distribution

After doses of 0.1 and 0.2 mg/kg *NIMBEX* administered to healthy adult surgical patients volume of distribution at steady-state is 121 to 161 ml/kg.

##### Metabolism

Cisatracurium undergoes degradation in the body at physiological pH and temperature by Hofmann elimination (a chemical process) to form laudanosine and the monoquaternary acrylate metabolite. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite.

These metabolites do not possess neuromuscular blocking activity.

##### Elimination

Elimination of cisatracurium is largely organ-independent but the liver and kidneys are primary pathways for the clearance of its metabolites.

##### I.V. bolus injection

Pharmacokinetic parameters after doses of 0.1 and 0.2 mg/kg *NIMBEX* 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 |
| Elimination half-life | 22 to 29 min         |

##### I.V. infusion

The pharmacokinetics of cisatracurium after infusion are similar to those after single bolus injection. Pharmacokinetics were studied in healthy adult surgical patients who received an initial 0.1 mg/kg bolus dose of cisatracurium followed by a maintenance infusion of *NIMBEX* to maintain 89 to 99%  $T_1$  suppression. Mean clearance of cisatracurium was 6.9 ml/kg/min and elimination half-life was 28 min. The recovery profile after infusion of *NIMBEX* is independent of duration of infusion and is similar to that after single bolus injections.

##### Special Patient Populations

###### Elderly

There are no clinically important differences in the pharmacokinetics of cisatracurium in elderly and young adult patients. In a comparative study, plasma clearance was not affected by age. Minor differences in volume of distribution (+17%) and half-life (+4 min) did not affect the recovery profile (see *Dosage and Administration*).

###### 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. In a comparative study, there were no statistically significant or clinically important differences in pharmacokinetic parameters of *NIMBEX*. The recovery profile of *NIMBEX* is unchanged in the presence of renal failure (see *Dosage and Administration*).

###### 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. In a comparative study of patients undergoing liver transplantation and healthy adults, there were small differences in volume of distribution (+21%) and clearance (+16%), but no difference in elimination half-life of cisatracurium. The recovery profile was unchanged (see *Dosage and Administration*).

###### 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. Mean clearance of cisatracurium was 7.5 ml/kg/min and elimination half-life was 27 min. The recovery profile after infusions of *NIMBEX* in ICU patients is independent of duration of infusion.

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

#### Pre-clinical Safety Data

The mutagenic risk to patients undergoing muscle relaxation with *NIMBEX* is considered negligible.

Carcinogenicity studies have not been performed.

#### PHARMACEUTICAL PARTICULARS

##### List of Excipients

As registered locally.

##### Incompatibilities

*NIMBEX* is not chemically stable when diluted with 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, sodium thiopentone. It is not compatible with ketorolac trometamol or propofol injectable emulsion.

##### Shelf Life

The expiry date is indicated on the packaging.

##### Special Precautions for Storage

Store between 2°C and 8°C.

Protect from light.

Do not freeze.

*NIMBEX* contains no antimicrobial preservative therefore dilution should be carried out immediately prior to use and administration should commence as soon as possible thereafter. Any unused solution diluted in an infusion fluid, or remaining in a used vial or open ampoule, should be discarded.

##### Nature and Contents of Container

As registered locally.

##### Instructions for Use/Handling

Diluted *NIMBEX* is physically and chemically stable for at least 24 h between 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 polypropylene:

sodium chloride (0.9% w/v) i.v. infusion

glucose (5% w/v) i.v. infusion

sodium chloride (0.18% w/v) and glucose (4% w/v) i.v. infusion

sodium chloride (0.45% w/v) and glucose (2.5% w/v) i.v. 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* has been shown to be compatible with the following commonly used peri-operative drugs, when mixed in conditions simulating administration into a running i.v. 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*, it is recommended that each drug be flushed through with an adequate volume of a suitable i.v. fluid, e.g. sodium chloride i.v. infusion 0.9% (w/v).

As with other drugs administered intravenously, when a small vein is selected as the injection site, *NIMBEX* should be flushed through the vein with a suitable i.v. fluid, e.g. sodium chloride i.v. infusion (0.9% w/v).

Not all presentations are available in every country.

Manufactured by:  
GlaxoSmithKline Manufacturing S.p.A.  
Parma  
Italy

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