

Summary of Product Characteristics

NIMBEX*

cisatracurium besylate

1. TRADE NAME OF THE MEDICINAL PRODUCT

NIMBEX injection 2mg/ml.

NIMBEX [FORTE] injection 5mg/ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A sterile solution containing 2mg cisatracurium (bis-cation) per mL as cisatracurium besilate (BAN, pINN). The product contains no antimicrobial preservative and is supplied in an ampoule.

A sterile solution containing 5mg cisatracurium (bis-cation) per mL as cisatracurium besilate (BAN, pINN). The product contains no antimicrobial preservative and is supplied in a vial.

Chemical Description: NIMBEX (cisatracurium besilate), (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.

Cisatracurium besilate is one of the ten isomeric components of atracurium besilate comprising about 15% of the mixture.

3. PHARMACEUTICAL FORM

Solution for Injection.

4. CLINICAL PARTICULARS

NIMBEX is an intermediate-duration, non-depolarising neuromuscular blocking agent for intravenous administration.

4.1 Therapeutic Indications

NIMBEX is indicated for use during surgical and other procedures and in intensive care. NIMBEX can be 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.

4.2 Posology and Method of Administration

- Please note that NIMBEX should not be mixed in the same syringe or administered simultaneously through the same needle as propofol injectable emulsion, ketorolac trometamol or with alkaline solutions such as sodium thiopentone. (Please refer to section 6.2 for details of incompatibilities).

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

Monitoring advice: 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 intravenous bolus injection

Dosage in adults:

Tracheal Intubation: The recommended intubation dose of NIMBEX for adults is 0.15mg/kg (body weight), administered rapidly over 5 to 10 seconds. This dose produced good to excellent conditions for tracheal intubation 120 seconds after administration of NIMBEX, following induction of anaesthesia.

Higher doses will shorten the time to onset of neuromuscular block. The following table summarises mean pharmacodynamic data when NIMBEX was administered at doses of 0.1 to 0.4mg/kg (body weight) to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

Initial NIMBEX Dose mg/kg (body weight)	Anaesthetic Background	Time to 90% T ₁ * Suppression (min)	Time to Maximum T ₁ * Suppression (min)	Time to 25% 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

* T₁ 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 0.03mg/kg (body weight) 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 administered. 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 readily reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T₄:T₁ ratio ≥ 0.7) are approximately 2 and 5 minutes respectively, following administration of the reversal agent at an average of 13% T₁ recovery.

Dosage in paediatric patients:

Tracheal Intubation (paediatric patients aged 1 month to 12 years): As in adults, the recommended intubation dose of NIMBEX is 0.15mg/kg (body weight) 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

NIMBAX Dose mg/kg (body weight)	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

NIMBAX Dose mg/kg (body weight)	Anaesthetic Background	Time to 90% Suppression (min)	Time to Maximum Suppression (min)	Time to 25% Spontaneous T ₁ Recovery (min)
0.15	Halothane	2.3	3.0	43
0.15	Opioid	2.6	3.6	38

The above dose has not been studied for intubation in ASA Class III-IV paediatric patients.

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 0.1 mg/kg for paediatric patients aged 2 to 12 years are presented in the table below:

NIMBEX Dose mg/kg (body weight)	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

Administration of NIMBEX following suxamethonium has not been studied in paediatric patients (see section 4.5 Interaction with Other Medicaments and Other Forms of Interaction).

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 anaesthesia with other halogenated fluorocarbon anaesthetic agents, but these agents may also be expected to extend the clinically effective duration of a dose of NIMBEX.

Maintenance (paediatric patients aged 2-12 years).

Neuromuscular block can be extended with maintenance doses of NIMBEX. In paediatric patients aged 2 to 12 years, a dose of 0.02mg/kg (body weight) provides approximately 9 minutes of additional clinically effective neuromuscular block during halothane anaesthesia. Consecutive maintenance doses do not result in progressive prolongation of effect.

There are insufficient data to make a specific recommendation for maintenance dosing in paediatric patients under 2 years of age. However, very limited data from clinical studies in paediatric patients under 2 years of age suggest that a maintenance dose of 0.03mg/kg may extend clinically effective neuromuscular block for a period of up to 25 minutes during opioid anaesthesia.

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 readily reversible with standard doses of anti-cholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T₄:T₁ ratio ≥ 0.7) are approximately 2 and 5 minutes respectively, following administration of the reversal agent at an average of 13% T₁ recovery.

Use by intravenous infusion:

Dosage in adults and pediatric patients aged 1 month to 12 years:

Maintenance of neuromuscular block may be achieved by infusion of NIMBEX. An initial infusion rate of 3 μg/kg (body weight)/min (0.18mg/kg/hr) is recommended to restore 89 to 99% T₁ suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 to 2 μg/kg (body weight)/min (0.06 to 0.12mg/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 is administered during isoflurane or enflurane anaesthesia. (See Section 4.5).

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.

Infusion delivery rate of NIMBEX injection 2mg/ml

Patient (body weight) (kg)	Dose (μ g/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

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 pediatric patients under 2 years of age, extrapolation of pharmacodynamic data for bolus doses suggests that NIMBEX infusion rates should be similar.

Dosage in neonates aged less than 1 month:

The use of NIMBEX in neonates is not recommended as it has not been studied in this patient population.

Dosage in elderly patients:

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.

Dosage in 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.

Dosage in 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.

Dosage in patients with cardiovascular disease:

When administered by rapid bolus injection (over 5 to 10 seconds) to adult patients with serious cardiovascular disease (New York Heart Association Class I-III) undergoing coronary artery bypass graft (CABG) surgery, NIMBEX has not been associated with clinically significant cardiovascular effects at any dose studied (up to and including 0.4 mg/kg ($8 \times ED_{95}$)). However, there are limited data for doses above 0.3 mg/kg in this patient population).

Dosage in Intensive Care Unit (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 μ g/kg (body weight)/min (0.18mg/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 μ g/kg/min [range 0.5 to 10.2 μ g/kg (body weight)/min (0.03 to 0.6mg/kg/hr)]

The median time to full spontaneous recovery following long-term (up to 6 days) infusion of NIMBEX in ICU patients was approximately 50 minutes.

Infusion delivery rate of NIMBEX FORTE injection 5mg/ml

Patient (body weight) (kg)	Dose (μ g/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 to ICU patients is independent of duration of infusion.

4.3 Contra-indications:

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

-NIMBEX is contra-indicated in pregnancy since there is no information on the use of NIMBEX in pregnant women.

-NIMBEX is contra-indicated in neonates aged less than 1 month since it has not been studied in this patient population.

4.4 Special Warnings and Special Precautions for Use:

Product specific topics.

Cisatracurium 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 have to be available.

Great caution should be exercised when administering NIMBEX 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 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 0.02mg/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.

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

There have been no studies of cisatracurium 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.

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.

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

Intensive Care Unit (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. In the most sensitive animal species, these effects occurred at laudanosine plasma concentrations similar to those that have been observed in some ICU patients following prolonged infusion of atracurium.

Consistent with the decreased infusion rate requirements of cisatracurium, 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 (eg. cranial trauma, hypoxic encephalopathy, cerebral oedema, viral encephalitis, uraemia). A causal relationship to laudanosine has not been established.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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: By anaesthetic agents such as enflurane, isoflurane, halothane (see section 4.2) and ketamine, by other non-depolarising neuromuscular blocking agents or by other drugs such as antibiotics (including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin), antiarrhythmic drugs (including propranolol, calcium channel blockers, lignocaine, procainamide and quinidine), diuretics, (including frusemide and possibly thiazides, mannitol and acetazolamide), magnesium and lithium salts and ganglion blocking drugs

(trimetaphan, hexamethonium).

-Decreased effect: is seen after 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 myasthenia syndrome; increased sensitivity to non-depolarising neuromuscular blocking agents might result. Such drugs include various antibiotics, β -blockers (propranolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), antirheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

4.6 Pregnancy and Lactation

NIMBEX is contra-indicated in pregnancy since there is no information on the use of NIMBEX in pregnant women. Fertility studies have not been performed. Reproduction studies in rats have not revealed any adverse effects on foetal development of cisatracurium. The relevance of these studies is limited due to species differences in metabolism and low systemic exposure levels.

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

4.7 Effects on Ability to Drive and Use Machines

This precaution is not relevant to the use of NIMBEX. However the usual precautions relating to performance of tasks following general anaesthesia still apply.

4.8 Undesirable Effects

Adverse experiences considered possibly attributable occurred with a frequency of less than 0.5%. These were cutaneous flushing or rash, bradycardia, hypotension and bronchospasm (see sections 4.2 and 5.1). 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.

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.

4.9 Overdosage

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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 $8 \times ED_{95}$.

Mode of action: 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 anti-cholinesterase 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 0.05mg/kg bodyweight during opioid anaesthesia (thiopentone/fentanyl/midazolam).

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

5.2 Pharmacokinetic Properties

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

Population pharmacokinetic modelling confirms and extends these findings up to 0.4mg/kg ($8 \times ED_{95}$). Pharmacokinetic parameters after doses of 0.1 and 0.2mg/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
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, In a comparative study, plasma clearance was not affected by age. Minor differences in volume of distribution (+ 17%) and half-life (+4min.) did not affect the recovery profile (see 4.2 Posology and Method of Administration).

The recovery profile is also unchanged.

Pharmacokinetics in patients with renal/hepatic impairment: There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage renal failure or end stage liver disease and in healthy adult patients. In a comparative study, there were no statistically significant or clinically important differences in pharmacokinetic parameters of cisatracurium and 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 differences in elimination half-life of cisatracurium.

Their recovery profiles are also unchanged.

Pharmacokinetics during infusions: The pharmacokinetics of cisatracurium after infusions of NIMBEX are similar to those after single bolus injection.

Pharmacokinetics were studied in healthy adult surgical patients who received an initial 0.1 mg/kg (body weight) bolus dose of NIMBEX followed by a maintenance infusion of NIMBEX to maintain 89 to 99% T₁ 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 injection.

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. 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 Section 4.4). These metabolites do not contribute to neuromuscular block.

5.3 Preclinical Safety Data

Acute toxicity: Meaningful acute studies with cisatracurium could not be performed. For symptoms of toxicity see "Overdosage".

Subacute Toxicity: Studies with repeated administration for three weeks in dogs and monkeys showed no compound specific toxic signs.

Mutagenicity: Cisatracurium was not mutagenic in an in vitro microbial mutagenicity test at concentrations up to 5000 μ g/plate.

In an in vivo cytogenetic study in rats, no significant chromosomal abnormalities were seen at S.C doses up to 4mg/kg.

Cisatracurium was mutagenic in an in vitro mouse lymphoma cell mutagenicity assay, at concentrations of 40 μ g/ml and higher.

A single positive mutagenic response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Carcinogenicity: Carcinogenicity studies have not been performed.

Local tolerance: The result of an intra-arterial study in rabbits showed that NIMBEX injection is well tolerated and no drug related changes were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Benzenesulfonic Acid solution, 32% w/v (Wellcome specification) Water for Injections (Ph.Eur).

6.2 Incompatibilities

Degradation of cisatrilcurium besilate has been demonstrated to occur more rapidly in lactated Ringer's Injection and 5% Dextrose and lactated Ringer's Injection than in the infusion fluids listed under Section 6.6.

Therefore it is recommended that lactated Ringer's Injection and 5% Dextrose and lactated Ringer's Injection are not used as the diluent in preparing solutions of NIMBEX for infusion.

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, e.g., sodium thiopentone. It is not compatible with ketorolac trometamol or propofol injectable emulsion.

6.3 Shelf-Life

Shelf-life of the medicinal product as packaged for sale:- 24 months at 2 -8°C.

Shelf-life after dilution according to directions:- The product contains no antimicrobial preservative and therefore should be used immediately on dilution, or failing this the aseptically prepared dilution should be stored at 2-8°C for no more than 24 hours, after which time unused solution should be discarded.

Shelf-life after the first time the pack is opened:- The pack is designed for use on a single occasion, injected or diluted immediately after opening, any remaining solution should be discarded.

6.4 Special Precautions for Storage

Do not freeze.

Protect from light.

6.5 Nature and Contents of Container

Nimbex injection 2mg/ml comes in boxes of 5×2.5ml, 5ml or 10ml ampoules and Nimbex [Forte] injection 5mg/ml as 1×30ml vial.(not available in Iran)

6.6 Instructions for Use/Handling

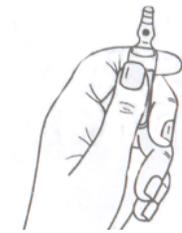
- Use only clear and almost colourless up to slightly yellow/greenish yellow coloured solutions.
- Diluted NIMBEX is physically and chemically stable for at least 24 hours at 5 ° C and 25 ° C at the concentration between 0.1 and 2 mg/mL in the following infusion fluids, in either polyvinyl chloride or 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, or failing this be stored as directed under section 6.3.

Instructions to open the ampoule

Ampoules are equipped with the OPC (One Point Cut) opening system and must be opened following the below instructions:

- hold with the hand the bottom part of the ampoule as indicated in picture n. 1
- put the other hand on the top of the ampoule positioning the thumb above the coloured point and press as indicated in picture n. 2



Picture 1



Picture 2

NIMBEX 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, 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).

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 intravenous fluid, e.g., Sodium Chloride Intravenous Infusion (0.9% w/v).

GlaxoWellcome

*Trade mark

Glaxo Wellcome S.p.A., Parma, Italy