Neuromuscular Blockade in the ICU

NIMBEX Indication

NIMBEX® (cisatracurium besylate) is an intermediate-onset/intermediate-duration neuromuscular blocking agent indicated for inpatients and outpatients as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation in the ICU.

Safety Considerations

NIMBEX is contraindicated in patients with known hypersensitivity to the product and its components. Severe anaphylactic reactions to neuromuscular blocking agents, including NIMBEX, have been reported. The 10-mL multiple-dose vials of NIMBEX contain benzyl alcohol, which is contraindicated for use in premature infants and is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity and there have been rare reports of deaths, primarily in preterm infants. NIMBEX is not recommended for rapid sequence endotracheal intubation, will not counteract bradycardia, and requires individualized dosing for conditions causing potentiation of or resistance to neuromuscular block. Certain drugs may potentiate the neuromuscular blocking action of the drug.

Please see Important Safety Information on page 6.

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Neuromuscular Blockers (NMBs) May Be Used in the ICU for:

- Facilitating mechanical ventilation by stopping spontaneous breathing efforts and preventing patient-ventilator dyssynchrony

Safety Considerations:

- Severe anaphylactic reactions to neuromuscular blocking agents, including NiMBex, have been reported. These reactions have in some cases been life-threatening and fatal. Precaution should be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents.

- NiMBex should only be administered intravenously, in carefully adjusted dosage by, or under the supervision of, experienced clinicians familiar with the drug’s actions and possible complications.

- The use of NiMBex in the ICU for longer than 6 days has not been studied. Long-term infusion (up to 6 days) of NiMBex during mechanical ventilation in the ICU has been safely used in two studies.

- Adverse experiences were uncommon among the 68 ICU patients who received NiMBex in conjunction with other drugs in US and European clinical studies. One out of 68 patients experienced bronchospasm. In one study, there were 2 reports of prolonged recovery among 28 patients administered NiMBex compared with 13 reports among 30 patients administered vecuronium.

ICU patients may be mechanically ventilated for the following reasons:

- Acute respiratory distress syndrome (ARDS)
- Pneumonia
- Bacteremia/sepsis
- Head trauma
- Intracranial hemorrhage
- Blunt/penetrating chest or abdominal trauma
- Post-operative complications
- Therapeutic hypothermia³

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**Important Considerations When Caring for a Patient on a Neuromuscular Blocker**

The ICU patient on a neuromuscular blocking agent is completely paralyzed (i.e., unable to breathe, cannot blink, no swallowing or gag reflex, etc.). They are dependent on the ICU team to protect them from potential complications. The following are recommendations to provide patient safety:

- Provide adequate sedation and analgesia (NMBs have no sedative or analgesic properties; always use with a sedative for amnesia to minimize patient recall)
- Use a twitch monitor to assess the patient’s train-of-four responses and document the level of paralysis
- Always deliver the lowest effective dose of the NMB; to ensure the dose is not excessive, allow some muscle stimulation to occur
- Protect the patient’s eyes with the use of artificial tears
- Position the patient so as to protect pressure points
- Address deep vein thrombosis
  - Sequential compression boots
  - Chemical anticoagulation
- Prevent stress ulcers
- Administer mouth washes
- Elevate the head of the bed to prevent ventilator-associated pneumonia
- Monitor pupillary reflexes to assess neurologic status
- Schedule a neuromuscular blocker “holiday” every 12-24 hours to assess need for continued use
Why Monitoring Is Important

Close monitoring of patients receiving NMBs is important for several reasons:

- To assess the depth and duration of neuromuscular blockade, which can vary from patient to patient
- To help determine when additional doses are needed
- To assess recovery from the block
- To prevent overdose

Monitoring With Train of Four

Monitoring a patient’s responses to a series of four peripheral-nerve stimuli (“train of four”) can help you assess the degree of neuromuscular blockade.
How to Monitor With Train of Four

How It Works:

• A battery-powered stimulator delivers a small electric current to a superficial nerve, usually the ulnar nerve
• Activity stimulated by the four consecutive impulses is assessed by watching or feeling for associated muscle movement
• The muscle movement (“twitch”) observed is used to estimate the level of blockade (see the chart below)

Things to Keep in Mind:

• Adequate muscle relaxation exists when 2 of 4 twitches are present
• Good intubating conditions exist when 1 of 4 twitches remains
• It is important to take the patient off the NMB periodically to determine if it is still needed

### Train-of-Four Responses

<table>
<thead>
<tr>
<th>Response</th>
<th>Approximate % of Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four twitches</td>
<td>0-75</td>
</tr>
<tr>
<td>Three twitches</td>
<td>75</td>
</tr>
<tr>
<td>Two twitches</td>
<td>80</td>
</tr>
<tr>
<td>One twitch</td>
<td>90</td>
</tr>
<tr>
<td>Twitches absent</td>
<td>100</td>
</tr>
</tbody>
</table>
NiMBex: Overview

Indication

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NiMBex Pharmacokinetics

NiMBex Elimination
- NiMBex is cleared from the body primarily through organ-independent Hofmann elimination (a chemical process dependent on pH and temperature).

NiMBex Hemodynamic Profile
- NiMBex does not cause dose-related increases in histamine concentration.
  - A study by Lien et al. comparing equipotent doses of atracurium and NiMBex in healthy patients showed no histamine release (up to and including 8 x ED$_{95}$) when administered over 5 to 10 seconds.\(^4\)
- NiMBex does not cause dose-related effects on mean arterial blood pressure or heart rate.
  - In a study by Searle et al. comparing NiMBex and vecuronium, the rapid administration of NiMBex (at doses up to 4 x ED$_{95}$) administered over 5 to 10 seconds did not cause hemodynamic side effects in patients with CAD.\(^5\)
- Severe anaphylactic reactions to neuromuscular blocking agents, including NiMBex, have been reported. These reactions have in some cases been life-threatening and fatal. Precaution should be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents.
Neuromuscular Duration and Recovery:

A prospective, randomized, double-blind study compared the infusion requirements and recovery profiles of NiMBex and vecuronium in ICU patients.¹,⁶

**Findings:**

- Average neuromuscular recovery time ($P=0.02$)
  - NiMBex: 68±13 minutes
  - Vecuronium: 387±163 minutes

- Reports of prolonged recovery ($P=0.002$)
  - NiMBex: 2 of 28 (7%)
  - Vecuronium: 13 of 30 (43%)

**Safety Considerations¹**

When using NiMBex in the ICU, it is recommended that neuromuscular function be monitored with a nerve stimulator.

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**Pharmacodynamics: NMB, Duration of Infusion, and Recovery Times After NMB Infusion**

- **Mean Duration of NMB Infusion** ($P=0.34$)
  - NiMBex: 80±7 minutes (n=28)
  - Vecuronium: 387±163 minutes (n=30)

- **Mean Time to $>70\%$ TOF** ($P=0.02$)
  - NiMBex: 68±12 minutes (n=20)
  - Vecuronium: 58±7 minutes (n=12)

- **Median Time to $>70\%$ TOF**
  - NiMBex: 66±12 minutes (n=20)
  - Vecuronium: 178 minutes (n=12)

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NiMBex Dosing Guidelines

In the ICU, NiMBex is indicated to facilitate mechanical ventilation.

Infusion Rates and Duration in the ICU¹:

• Average infusion rates of approximately 3 mcg/kg/min (range: 0.5 to 10.2) should provide adequate neuromuscular block in adults

• Long-term infusion of NiMBex (up to 6 days) during mechanical ventilation in the ICU has been evaluated in 2 studies. The use of NiMBex in the ICU for longer than 6 days has not been studied.

Safety Considerations¹

Dosage requirements may increase or decrease with time. Additional doses of NiMBex or any other neuromuscular blocking agent should not be given before there is a definite response to nerve stimulation. If no response is elicited, infusion administration should be discontinued until a response returns.
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Important Safety Information

- NIMBEX is contraindicated in patients with known hypersensitivity to the product and its components. The 10-mL multiple-dose vials of NIMBEX are contraindicated for use in premature infants because the formulation contains benzyl alcohol.
- Severe anaphylactic reactions to neuromuscular blocking agents, including NIMBEX, have been reported. These reactions have in some cases been life-threatening and fatal. Precaution should be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents.
- NIMBEX should only be administered intravenously in carefully adjusted dosage by or under the supervision of experienced clinicians familiar with the drug’s actions and possible complications.
- It is recommended that a peripheral nerve stimulator be used during the administration of NIMBEX to monitor drug effect, determine the need for additional doses, and confirm recovery from neuromuscular block.
- NIMBEX has no known effect on consciousness, pain threshold, or cerebration.
- The 10-mL multiple-dose vials of NIMBEX contain benzyl alcohol, which is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity, particularly in preterm infants and neonates, and there have been rare reports of deaths, primarily in preterm infants. The minimum amount of benzyl alcohol at which toxicity may occur is not known. The practitioner must consider the daily metabolic load of benzyl alcohol from medications containing this preservative. Single-use vials (5-mL and 20-mL) of NIMBEX do not contain benzyl alcohol. NIMBEX has not been studied in pediatric patients below the age of 1 month.
- NIMBEX has an intermediate onset of action and is not recommended for rapid sequence endotracheal intubation.
- NIMBEX will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.
- Doses should be individualized for conditions causing potentiation of or resistance to neuromuscular block, such as in patients with neuromuscular diseases, burns, hemiparesis or paraparesis, acid-base and/or serum electrolyte abnormalities, and in patients receiving chronic treatment with phenytoin or carbamazepine.

Please click here for full Prescribing Information.
• Long-term infusion (up to 6 days) of NIMBEX during mechanical ventilation in the ICU has been safely used in 2 studies. Use in the ICU for longer than 6 days has not been studied. Dosage requirements may increase or decrease with time. Whenever the use of NIMBEX in the ICU is contemplated, it is recommended that neuromuscular function be monitored during administration with a nerve stimulator. Additional doses of NIMBEX or any other neuromuscular blocking agent should not be given before there is a definite response to nerve stimulation. If no response is elicited, infusion administration should be discontinued until a response returns.

• The time to onset of maximum block following NIMBEX is approximately 2 minutes faster with prior administration of succinylcholine.

• Isoflurane or enfurane administered with nitrous oxide/oxygen to achieve 1.25 MAC may prolong the clinically effective duration of action and decrease the required infusion rate of NIMBEX. Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as NIMBEX include certain antibiotics (e.g., aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistemethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine.

• No adverse event was reported by >1% of the surgical patients treated with NIMBEX during clinical trials; <1% of patients reported bradycardia, hypotension, flushing, bronchospasm, and/or rash.

• Adverse experiences were uncommon among the 68 ICU patients who received NIMBEX in conjunction with other drugs in US and European clinical studies. One out of 68 patients experienced bronchospasm. In one study, there were 2 reports of prolonged recovery among 28 patients administered NIMBEX compared with 13 reports among 30 patients administered vecuronium.

References: