

Final Core Safety Profile
vecuronium bromide
Procedure CZ/H/PSUR/0002/002.
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4.3 Contraindications

Hypersensitivity to vecuronium or the bromide ion or to any of the excipients of Norcuron.

4.4 Special warnings and precautions for use

Since <Product Name> causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored.

As with other neuromuscular blocking agents, residual curarization has been reported for Norcuron. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Other factors which could cause residual curarization after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal agent should be considered, especially in those cases where residual curarization is more likely to occur.

Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross-reactivity to neuromuscular blocking agents has been reported.

Since <Product Name> has no cardiovascular effects within the clinical dosage range, it does not attenuate bradycardia that may occur due to the use of some types of anesthetics and opiates or due to vagal reflexes during surgery. Therefore, reassessment of the use and/or dosage of vagolytic drugs such as atropine for premedication or at induction of anesthesia, may be of value for surgical procedures during which vagal reactions are more likely to occur (e.g. surgical procedures where anesthetic drugs with known vagal stimulatory effects are used, ophthalmic, abdominal or anorectal surgery, etc.).

In general, following long term use of neuromuscular blocking agents in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdose it is strongly recommended that neuromuscular transmission is monitored throughout the use of neuromuscular blocking agents. In addition, patients should receive adequate analgesia and sedation. Furthermore, neuromuscular blocking agents should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Myopathy after long term administration of non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported frequently. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of the neuromuscular blocking agent should be limited as much as possible.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Norcuron:

Hepatic and/or biliary tract disease and renal failure

Because vecuronium is excreted in bile and in urine, <Product Name> should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed, especially when high doses of vecuronium (0.15-0.2 mg/kg bodyweight) were administered in patients with hepatic disease.

Prolonged circulation time

Conditions associated with prolonged circulation time such as cardiovascular disease, old age, oedematous state resulting in an increased volume of distribution, may contribute to an increase in the onset time of neuromuscular block. The duration of action may also be prolonged due to a reduced plasma clearance.

Neuromuscular disease

As with other neuromuscular blocking agents, <Product Name> should be used with extreme caution in patients with neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or the myasthenic (Eaton Lambert) syndrome, small doses of <Product Name> may have profound effects and <Product Name> should be titrated to the response.

Hypothermia

In operations under hypothermia, the neuromuscular blocking effect of <Product Name> is increased and the duration is prolonged.

Obesity

Like other neuromuscular blocking agents, <Product Name> may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight.

Burns

Patients with burns are known to develop resistance to non-depolarizing agents. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of <Product Name> are:

Hypokalaemia (e.g. after severe vomiting, diarrhoea, and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnoea, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

4.5 Interaction with other medicinal products and other forms of interaction

The following drugs have been shown to influence the magnitude and/or duration of action of non-depolarizing neuromuscular blocking agents:

Effect of other drugs on Norcuron

Increased effect:

Halogenated volatile anesthetics potentiate the neuromuscular block of Norcuron. The effect only becomes apparent with maintenance dosing (see also section 4.2). Reversal of the block with anticholinesterase inhibitors could also be inhibited.

After intubation with suxamethonium (see section 4.2). Long-term concomitant use of corticosteroids and <Product Name> in the ICU may result in prolonged duration of neuromuscular block or myopathy (see also section 4.4 and 4.8).

Other drugs

□ antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.

□ diuretics, quinidine, magnesium salts, calcium channel blocking agents, lithium salts, cimetidine, lidocaine and acute administration of phenytoin or β -blocking agents.

Recurarization has been reported after post-operative administration of:

aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine and magnesium salts (see section 4.4).

Decreased effect:

Prior chronic administration of phenytoin or carbamazepine.

Variable effect:

Administration of other non-depolarizing neuromuscular blocking agents in combination with <Product Name> may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.

Suxamethonium given after the administration of <Product Name> may produce potentiation or attenuation of the neuromuscular blocking effect of Norcuron.

Effect of <Product Name> on other drugs

Effect of <Product Name> on lidocaine

<Product Name> combined with lidocaine may result in a quicker onset of action of lidocaine.

4.6 Fertility, pregnancy and lactation

Fertility:

Animal studies do not indicate an effect on fertility.

There are insufficient data on the use of <Product Name> during animal or human pregnancy to assess potential harm to the foetus. <Product Name> should be given to a pregnant woman only when the attending physician decides that the benefits outweigh the risks.

Cesarean section

Studies with Norcuron, administered in doses up to 0.1 mg/kg, have shown its safety for use in cesarean section. In cesarean section the dose should not exceed 0.1 mg/kg.

In several clinical studies <Product Name> did not affect Apgar score, fetal muscle tonus or cardiorespiratory adaptation. From umbilical cord blood sampling it is apparent that only very little placental transfer of <Product Name> occurs which did not lead to the observation of any clinical adverse effect in the new-born.

Note:

Reversal of Norcuron-induced neuromuscular block may be inhibited or unsatisfactory in patients receiving magnesium sulphate for toxemia of pregnancy because magnesium salts enhance neuromuscular block.

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Therefore, in patients receiving magnesium sulphate, the dosage of <Product Name> should be reduced and be carefully titrated to twitch response.

Lactation

There are no human data on the use of <Product Name> during lactation. <Product Name> should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

4.7 Effects on ability to drive and use machines

Since <Product Name> is used as an adjunct to general anesthesia, the usual precautionary measures after a general anesthesia should be taken for ambulatory patients.

4.8 Undesirable effects

Adverse Drug Reactions (ADRs) are rare (< 1/1000). The most commonly occurring ADRs include changes in vital signs and prolonged neuromuscular block. The most frequently reported ADR during post-marketing surveillance is ‘anaphylactic and anaphylactoid reactions’ and associated symptoms (reporting frequency <1/100 000). See also the explanations below the table.

MedDRA SOC	Preferred term ¹	
	Uncommon/rare (<1/100, >1/10 000)	Very rare (<1/10 000)
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock
Nervous system disorders		Flaccid paralysis
Cardiac disorders	Tachycardia	
Vascular disorders	Hypotension	Circulatory collapse and shock Flushing
Respiratory, thoracic and mediastinal disorders		Bronchospasm

¹ Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.

MedDRA SOC	Preferred term ¹	
	Uncommon/rare (<1/100, >1/10 000)	Very rare (<1/10 000)
Skin and subcutaneous tissue disorders		Angioneurotic edema Urticaria Rash Erythematous rash
Musculoskeletal and connective tissue disorders		Muscular weakness ² Steroid myopathy ²
General disorders and administration site conditions	Drug ineffective Decreased drug effect/ therapeutic response Increased drug effect/ therapeutic response	Face oedema Injection site pain Injection site reaction
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anaesthesia

² after long-term use in the ICU

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Prolonged Neuromuscular block

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. A few cases of myopathy have been reported after <Product Name> was used in the ICU in combination with corticosteroids (see section 4.4).

Anaphylactic reactions

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Norcuron, have been reported. Anaphylactic/anaphylactoid reactions usually comprise of several signs or symptoms e.g. bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse – shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume they may occur and take the necessary precautions.

Histamine release and histaminoid reactions

Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematous reactions at the site of injection and/or generalized histaminoid (anaphylactoid) reactions (see also under anaphylactic reactions above) should always be taken into consideration when administering these drugs.

Experimental studies with intradermal injection of <Product Name> have demonstrated that this drug has only a weak capacity for inducing local histamine release. Controlled studies in man failed to demonstrate any significant rise in plasma histamine levels after intravenous administration of Norcuron. Still, such cases have rarely been reported during large scale use of Norcuron.

4.9 Overdose

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. In this situation there are two options for the reversal of neuromuscular block: (1) sugammadex can be used for reversal of intense (profound) and deep block. The dose of Sugammadex to be administered depends on the level of neuromuscular block. The use of Sugammadex for the purposes of reversal of vecuronium-induced blockade is recommended for use only in the adult population. (2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) can be used once spontaneous recovery starts and should be administered in adequate doses. When administration of a cholinesterase inhibitor fails to reverse the neuromuscular effect of Norcuron, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of a cholinesterase inhibitor can be dangerous.”