<table>
<thead>
<tr>
<th>Core Safety Profile</th>
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<tbody>
<tr>
<td><strong>Active substance:</strong></td>
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<tr>
<td><strong>Pharmaceutical form(s)/strength:</strong></td>
</tr>
<tr>
<td><strong>P-RMS:</strong></td>
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<tr>
<td><strong>Date of FAR:</strong></td>
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</tbody>
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4.3 Contraindications
Hypersensitivity to rocuronium or to the bromide ion or to any of the excipients.

4.4 Special warnings and precautions for use
Since rocuronium bromide causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique.

As with other neuromuscular blocking agents, residual curarization has been reported for rocuronium bromide. 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 reversal agent (such as sugammadex or acetylcholinesterase inhibitors) 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.

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 overdosage 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 other non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported regularly. 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.

If suxamethonium is used for intubation, the administration of rocuronium bromide should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of rocuronium bromide:
Hepatic and/or biliary tract disease and renal failure

Because rocuronium is excreted in urine and bile, it 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 with doses of 0.6 mg.kg\(^{-1}\) rocuronium bromide.

Prolonged circulation time

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

Neuromuscular disease

Like other neuromuscular blocking agents, rocuronium bromide 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 with the myasthenic (Eaton-Lambert) syndrome, small doses of rocuronium bromide may have profound effects and rocuronium bromide should be titrated to the response.

Hypothermia

In surgery under hypothermic conditions, the neuromuscular blocking effect of rocuronium bromide is increased and the duration prolonged.

Obesity

Like other neuromuscular blocking agents, rocuronium bromide 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 neuromuscular blocking agents. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of rocuronium bromide

Hypokalaemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, 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 rocuronium bromide

Increased effect

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

- After intubation with suxamethonium (see section 4.4).

- Long-term concomitant use of corticosteroids and rocuronium bromide in the ICU may result in prolonged duration of neuromuscular block or myopathy (see section 4.4 and 4.8).

Other drugs

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

- Diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anesthetics (lidocaine i.v, bupivacaine epidural) and acute administration of phenytoin or β-blocking agents.

Recurrence has been reported after post-operative administration of:
aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see section 4.4).

Decreased effect

- Prior chronic administration of phenytoin or carbamazepine.

- Protease inhibitors (gabexate, ulinastatin).

Variable effect

- Administration of other non-depolarizing neuromuscular blocking agents in combination with rocuronium bromide 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 rocuronium bromide may produce potentiation or attenuation of the neuromuscular blocking effect of rocuronium bromide.

Effect of rocuronium bromide on other drugs

Rocuronium bromide combined with lidocaine may result in a quicker onset of action of lidocaine.

Paediatric patients

No formal interaction studies have been performed. The above mentioned interactions for adults and their special warnings and precautions for use (see section 4.4) should also be taken into account for paediatric patients.
4.6 Pregnancy and lactation

**Pregnancy**

For rocuronium bromide, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing rocuronium bromide to pregnant women.

**Cesarean section**

In patients undergoing Cesarean section, rocuronium bromide can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anesthetic agent is administered or following suxamethonium facilitated intubation. Rocuronium bromide, administered in doses of 0.6 mg.kg\(^{-1}\), has been shown to be safe in parturients undergoing Cesarean section. Rocuronium bromide does not affect Apgar score, fetal muscle tone nor cardiorespiratory adaptation. From umbilical cord blood sampling it is apparent that only limited placental transfer of rocuronium bromide occurs which does not lead to the observation of clinical adverse effects in the newborn.

Note 1: doses of 1.0 mg.kg\(^{-1}\) have been investigated during rapid sequence induction of anesthesia, but not in Cesarean section patients. Therefore, only a dose of 0.6 mg.kg\(^{-1}\) is recommended in this patient group.

Note 2: reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of rocuronium bromide should be reduced and be titrated to twitch response.

**Lactation**

It is unknown whether rocuronium bromide is excreted in human breast milk. Animal studies have shown insignificant levels of rocuronium bromide in breast milk. Rocuronium bromide 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 rocuronium bromide 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

The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is ‘anaphylactic and anaphylactoid reactions’ and associated symptoms. See also the explanations below the table.
<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>Preferred term¹</th>
<th>Very rare (&lt;1/10 000)</th>
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<tbody>
<tr>
<td><strong>Uncommon/rare</strong>² (&lt;1/100, &gt;1/10 000)</td>
<td>Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock</td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Flaccid paralysis</td>
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<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
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<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
<td>Circulatory collapse and shock Flushing</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Angioneurotic edema Urticaria Rash Erythematous rash</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscular weakness³</td>
<td>Steroid myopathy³</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Drug ineffective Drug effect/ therapeutic response decreased Drug effect/ therapeutic response increased Injection site pain Injection site reaction</td>
<td>Face oedema</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Prolonged neuromuscular block Delayed recovery from anesthesia</td>
<td>Airway complication of anaesthesia</td>
</tr>
</tbody>
</table>

MedDRA version 8.1

¹ Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.
² Post-marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over two rather than five categories.
³ after long-term use in the ICU
Anaphylaxis

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including rocuronium bromide, have been reported. Anaphylactic/anaphylactoid reactions are: 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.

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.

In clinical studies only a slight increase in mean plasma histamine levels has been observed following rapid bolus administration of 0.3-0.9 mg.kg\(^{-1}\) rocuronium bromide.

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.

Myopathy

Myopathy has been reported after the use of various neuromuscular blocking agents in the ICU in combination with corticosteroids (see section 4.4).

Local injection site reactions

During rapid sequence induction of anesthesia, pain on injection has been reported, especially when the patient has not yet completely lost consciousness and particularly when propofol is used as the induction agent. In clinical studies, pain on injection has been noted in 16% of the patients who underwent rapid sequence induction of anesthesia with propofol and in less than 0.5% of the patients who underwent rapid sequence induction of anesthesia with fentanyl and thiopental.

Paediatric patients

A meta-analysis of 11 clinical studies in paediatric patients (n=704) with rocuronium bromide (up to 1 mg/kg) showed that tachycardia was identified as adverse drug reaction with a frequency of 1.4%.

4.9 Overdose

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. There are two options for the reversal of neuromuscular block: (1) In adults, 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. (2) An acetylcholinesterase inhibitor
(e.g. neostigmine, edrophonium, pyridostigmine) or sugammadex can be used once spontaneous recovery starts and should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of rocuronium bromide ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

In animal studies, severe depression of cardiovascular function, ultimately leading to cardiac collapse did not occur until a cumulative dose of 750 x ED90 (135 mg.kg\(^{-1}\) rocuronium bromide) was administered.