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Email: info@pharma-cell.com

2. Trade Name: Bronitine

3. Generic Name
Rocuronium Bromide 100 mg / 10 ml vial I.V. Infusion.

4. Composition
Each 10 ml Bronitine contains 100 mg rocuronium bromide. Excipients: contains Sodium acetate, Sodium chloride, Acetic acid and sodium hydroxide quantity sufficient and water for injection.

5. Pharmaceutical Form
Vial contains solution for I.V Infusion.

6. Pharmacological action
   Mechanism of Action:
   Bronitine (rocuronium bromide) is a fast onset, intermediate acting non-depolarising neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of drugs. It acts by competing for nicotinic cholinoreceptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

   Pharmacodynamic effects: The ED_{95} (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during intravenous anaesthesia is approximately 0.3 mg/kg rocuronium bromide. The ED_{95} in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg/kg respectively). The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with 0.6 mg/kg rocuronium bromide is 30–40 minutes. The total duration (time until spontaneous recovery to 90% of control twitch height) is 50 minutes. The mean time of spontaneous recovery of twitch response from 25 to 75% (recovery index) after a bolus dose of 0.6 mg/kg rocuronium bromide is 14 minutes. With lower dosages of 0.3-0.45 mg/kg rocuronium bromide (1-1½ x ED_{90}), onset of action is slower and duration of action is shorter. With high doses of 2 mg/kg, clinical duration is 110 minutes.

   Intubation during routine anaesthesia: Within 60 seconds following intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (2 x ED_{90} under intravenous anaesthesia), adequate intubation conditions can be achieved in nearly all patients of which in 80% intubation conditions are rated excellent. General muscle paralysis adequate for any type of procedure is established within 2 minutes. After administration of 0.45 mg/kg rocuronium bromide, acceptable intubation conditions are present after 90 seconds.

   Rapid Sequence Induction: During rapid sequence induction of anaesthesia under propofol or fentanyl/thiopental anaesthesia, adequate intubation conditions are achieved within 60 seconds in 93% and 96% of the patients respectively, following a dose of 1.0 mg/kg rocuronium bromide. Of these, 70% are rated excellent. The clinical duration with this dose approaches 1 hour, at which time the neuromuscular block can be safely reversed. Following a dose of 0.6 mg/kg rocuronium bromide, adequate intubation conditions are achieved within 60 seconds in 81% and 75% of the patients during a rapid sequence induction technique with propofol or fentanyl/thiopental, respectively.

   Special populations: Mean onset time in infants and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults. The duration of action of maintenance doses of 0.15 mg/kg rocuronium bromide might be somewhat longer under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic and/or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous anaesthesia (approximately 13 minutes). No accumulation of effect (progressive increase in duration of action) with repetitive maintenance dosing at the recommended level has been observed.

   Intensive Care Unit: Following continuous infusion in the Intensive Care Unit, the time to recovery of the train of four ratio to 0.7 depends on the level of block at the end of the infusion. After a continuous infusion for 20 hours or more the median (range) time between return of T2 to train of four stimulation and recovery of the train of four ratio to 0.7 approximates 1.5 (1-5) hours in patients without multiple organ failure and 4 (1-25) hours in patients with multiple organ failure.

   Cardiovascular surgery: In patients scheduled for cardiovascular surgery the most common cardiovascular changes during the onset of maximum block following 0.6-0.9 mg/kg rocuronium bromide are a slight and clinically
insignificant increase in heart rate up to 9% and an increase in mean arterial blood pressure up to 16% from the control values. 

Reversal of muscle relaxation: Administration of acetylcholinesterase inhibitors, (neostigmine, pyridostigmine or edrophonium) at reappearance of T2 or at the first signs of clinical recovery, antagonises the action of Bronitine.

7. Pharmacokinetic properties

After intravenous administration of a single bolus dose of rocuronium bromide the plasma concentration time course runs in three exponential phases. In normal adults, the mean (95%CI) elimination half-life is 73 (66-80) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193-214) ml/kg and plasma clearance is 3.7 (3.5-3.9) ml/kg/min.

In controlled studies the plasma clearance in geriatric patients and in patients with renal dysfunction was reduced, in most studies however without reaching the level of statistical significance. In patients with hepatic disease, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 ml/kg/min.

In infants (28 days to 23 months), the apparent volume of distribution at steady state conditions is increased compared to adults and children (2-11 years). In older children (3-8 yr), a trend is seen towards higher clearance and shorter elimination half-life (approximately 20 minutes) compared to adults, younger children and infants.

When administered as a continuous infusion to facilitate mechanical ventilation for 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A large between patient variability is found in controlled clinical studies, related to nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean (± SD) elimination half-life of 21.5 (± 3.3) hours, a (apparent) volume of distribution at steady state of 1.5 (± 0.8) l/kg and a plasma clearance of 2.1 (± 0.8) ml/kg/min were found.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours. After injection of a radiolabeled dose of rocuronium bromide, excretion of the radiolabel is on average 47% in urine and 43% in faeces after 9 days. Approximately 50% is recovered as the parent compound. No metabolites are detected in plasma.

8. Indications

Bronitine is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. Bronitine is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.

9. Dosage and administration

Like other neuromuscular blocking agents, Bronitine should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these drugs. As with other neuromuscular blocking agents, the dosage of Bronitine should be individualized in each patient. The method of anaesthesia and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other drugs that are administered concomitantly, and the condition of the patient should be taken into account when determining the dose.

The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery. Inhalational anaesthetics do potentiate the neuromuscular blocking effects of Bronitine. This potentiation however, becomes clinically relevant in the course of anaesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with Bronitine should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Bronitine during long lasting procedures (longer than 1 hour) under inhalational anaesthesia. In adult patients the following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the intensive care unit.

Surgical Procedures:

Tracheal intubation:

The standard intubating dose during routine anaesthesia is 0.6 mg/kg rocuronium bromide, after which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0 mg/kg rocuronium bromide is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia, after which adequate intubation conditions are established within 60 seconds in nearly all patients. If a dose of 0.6 mg/kg rocuronium bromide is used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide. For use of rocuronium bromide during rapid sequence induction of anaesthesia in patients undergoing Caesarean section reference is made to section 11.

Higher doses: Should there be reason for selection of larger doses in individual patients, there is no indication from clinical studies that the use of initial doses up to 2 mg/kg rocuronium bromide is associated with an increased frequency or severity of cardiovascular effects. The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of action.
**Maintenance dosing:** The recommended maintenance dose is 0.15 mg/kg rocuronium bromide; in the case of long-term inhalational anaesthesia this should be reduced to 0.075-0.1 mg/kg rocuronium bromide. The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height, or when 2 to 3 responses to train of four stimulation are present.

**Continuous infusion:** If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg/kg rocuronium bromide and, when neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 to 2 responses to train of four stimulation. In adults under intravenous anaesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6 mg/kg/h (300-600 micrograms/kg/h) and under inhalational anaesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

**Paediatric patients:** For infants (28 days–23 months), children (2-11 years) and adolescents (12–18 years) the recommended intubation dose during routine anaesthesia and maintenance dose are similar to those in adults. For continuous infusion in paediatrics, the infusion rates, with the exception of children, are the same as for adults. For children higher infusion rates might be necessary. For children the same initial infusion rates as for adults are recommended and this should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to train of four stimulation during the procedure. There are insufficient data to support dose recommendations for the use of rocuronium bromide in neonates (0-1 month). The experience with rocuronium bromide in rapid sequence induction in paediatric patients is limited. Rocuronium bromide is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

**Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure:** The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure is 0.6 mg/kg rocuronium bromide. A dose of 0.6 mg/kg should be considered for rapid sequence induction of anaesthesia in patients in which a prolonged duration of action is expected. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 mg/kg rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg/kg/h.

**Overweight and obese patients:** When used in overweight or obese patients (defined as patients with a body weight of 30% or more above ideal body weight) doses should be reduced taking into account ideal body weight.

**Intensive Care Procedures:**

**Tracheal intubation:**
For tracheal intubation, the same doses should be used as described above under surgical procedures.

**Maintenance dosing:** The use of an initial loading dose of 0.6 mg/kg rocuronium bromide is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train of four stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80-90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3-0.6 mg/kg/h during the first hour of administration, which will need to be decreased during the following 6-12 hours, according to the individual response. Thereafter, individual dose requirements remain relatively constant. A large between patient variability in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2-0.5 mg/kg/h depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Administration up to 7 days has been investigated.

**Special Populations:** **Bronitine** is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and geriatric patients due to a lack of data on safety and efficacy.

**Administration:** **Bronitine** is administered intravenously either as a bolus injection or as a continuous infusion.

**10. Contraindications**
Hypersensitivity to rocuronium or to the bromide ion or to any of the excipients.

**11. Side 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 term</th>
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<tr>
<td><strong>Uncommon/rare</strong></td>
<td><strong>Very rare (&lt;1/10 000)</strong></td>
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<td>(&lt;1/100, &gt;1/10 000)</td>
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<td>Immune system disorders</td>
<td>Hypersensitivity</td>
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<td>Anaphylactoid shock</td>
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<td>Nervous system disorders</td>
<td>Flaccid paralysis</td>
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<td>Cardiac disorders</td>
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<td>Vascular disorders</td>
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<td>Circulatory collapse and shock</td>
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<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscular weakness3</td>
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<td>Steroid myopathy3</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Drug ineffective</td>
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<td>Drug effect/ therapeutic response decreased</td>
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<td>Drug effect/ therapeutic response increased</td>
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<td>Injection site pain</td>
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<td>Injection site reaction</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Prolonged neuromuscular block</td>
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<td>Delayed recovery from anaesthesia</td>
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<td>Airway complication of anaesthesia</td>
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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

MedDRA version 8.1
Anaphylaxis

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, 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 erythematos reaction at the site of injection and/or generalised 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 rocuronium bromide.

Prolonged neuromuscular block

The most frequent adverse reaction to nondepolarising 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 anaesthesia, 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 anaesthesia with propofol and in less than 0.5% of the patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

12. Drug Interaction

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

Effect of other drugs on Bronitine:

Increased effect:
- Halogenated volatile anaesthetics potentiate the neuromuscular block of Bronitine. The effect only becomes apparent with maintenance dosing. Reversal of the block with anticholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium.
- Long-term concomitant use of corticosteroids and Bronitine in the ICU may result in prolonged duration of neuromuscular block or myopathy. Other drugs:
  - Antibiotics: aminoglycoside, lincomamide and polypeptide antibiotics, acylamino-penicillin antibiotics.
  - Diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lidocaine i.v, bupivacaine epidural) and acute administration of phenytoin or β-blocking agents. Recurcarisation has been reported after post-operative administration of: aminoglycoside, lincomamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts.

Decreased effect:
- Prior chronic administration of phenytoin or carbamazepine.
- Calcium chloride, potassium chloride.
- Protease inhibitors (gabexate, ulinastatin).

Variable effect:
- Administration of other non-depolarising neuromuscular blocking agents in combination with Bronitine 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 Bronitine may produce potentiation or attenuation of the neuromuscular blocking effect of Bronitine.

Effect of Bronitine on other drugs:
Bronitine combined with lidocaine may result in a quicker onset of action of lidocaine.
13. 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 Bronitine to pregnant women.

Caesarean section: In patients undergoing Caesarean section, Bronitine can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic agent is administered or following suxamethonium facilitated intubation. However, Bronitine, administered in doses of 0.6 mg/kg may not produce adequate conditions for intubation until 90 seconds after administration. This dose has been shown to be safe in parturients undergoing Caesarean section. Bronitine does not affect Apgar score, foetal muscle tone or 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 have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients. Therefore, only a dose of 0.6 mg/kg 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 Bronitine 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. Insignificant levels of rocuronium bromide were found in the milk of lactating rats. There are no human data on the use of Bronitine during lactation. Bronitine should be given to lactating women only when the attending physician decided that the benefits outweigh the risks.

14. Precautions and warning

Since Bronitine 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 neuromuscular blockade has been reported for Bronitine. In order to prevent complications resulting from residual neuromuscular blockade, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block.

Other factors which could cause residual neuromuscular blockade 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 neuromuscular blockade 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. Rocuronium may increase the heart rate.

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-depolarising 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 Bronitine 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 Bronitine:

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 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, Bronitine should be used with extreme caution in patients with a 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 Bronitine may
have profound effects and Bronitine should be titrated to the response.

Hypothermia: In surgery under hypothermic conditions, the neuromuscular blocking effect of Bronitine is increased
and the duration prolonged.

Obesity: Like other neuromuscular blocking agents, Bronitine 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-depolarising neuromuscular blocking agents. It is
recommended that the dose is titrated to response.

Conditions which may increase the effects of Bronitine: Hypokalaemia (e.g. after severe vomiting, diarrhoea and
diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration,
acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be
corrected when possible.

15. Package & Storage
Since Bronitine does not contain a preservative, the solution should be used immediately after opening the vial.

Bronitine 100 mg in 10 ml (10mg/ml), Packaging of 10 vials each containing 100 mg rocuronium bromide. Type I
Ph.Eur., clear, colourless, glass vial with a rubber closure and flip off cap. Store below 25 °C.

16. Instruction to Patient
Your anaesthetist needs to know before you receive this medicine:

- if you are allergic to muscle relaxants
- if you have had kidney, heart, liver or gall bladder disease
- if you have had diseases affecting nerves and muscles
- if you have fluid retention (oedema).

Tell your anaesthetist if any of these applies to you.

Some conditions may influence the effects of Bronitine — for example:

- low calcium levels in the blood
- low potassium levels in the blood
- high magnesium levels in the blood
- low levels of protein in the blood
- too much carbon dioxide in the blood
- loss of too much water from the body, for example by being sick, diarrhoea or sweating
- over-breathing leading to too little carbon dioxide in the blood (alkalosis)
- general ill-health
- burns
- being very overweight (obesity)
- very low body temperature (hypothermia).

If you have any of these conditions, your anaesthetist will take it into account when deciding the correct dose of
Bronitine for you.