NOVERON
Rocuronium Bromide
Solution for injection 10 mg/mL

COMPOSITION
Each ml contains Rocuronium bromide 10 mg.
Excipients: sodium chloride, sodium acetate, glacial acetic acid, water for injection.

PHARMACEUTICAL FORM
Solution for Injection
NOVERON is clear solution, colorless to yellow orange, practically free from visible particles without precipitation.
pH: 3.8 - 4.2
Osmolality: 250 - 350 mOsmol/kg.

MECHANISM OF ACTION
Noveron (rocuronium bromide) is a fast onset, intermediate acting non-depolarizing neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

INDICATION
Noveron is indicated as an adjunct to general anesthesia to facilitate endotracheal intubation, to provide skeletal muscle relaxation and to facilitate mechanical ventilation in adults, children and infants from one month of age.
Noveron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate mechanical ventilation as part of Rapid Sequence Induction, however, this has not been studied in infants and children

DOSAGE AND ADMINISTRATION
Like other neuromuscular blocking agents, Noveron 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 Noveron should be individualized in each patient. The method of anesthesia 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 anesthetics do potentiate the neuromuscular blocking effects of Noveron. This potentiation however, becomes clinically relevant in the course of anesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with Noveron should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Noveron during long lasting procedures (longer than 1 hour) under inhalational anesthesia (see section "Interaction with Other Medicinal Products and Other Forms of Interaction").
Risk of Medication Errors: Accidental administration of neuromuscular blocking agents may result in serious adverse events, including fatal outcomes. Store Noveron with the cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product (see section "Special Warnings and Precautions for Use").
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 anesthesia is 0.6 $mg.kg^{-1}$ rocuronium bromide, after which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0 $mg.kg^{-1}$ of rocuronium bromide is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anesthesia, after which adequate intubation conditions are established within 60 seconds in nearly all patients. If a dose of 0.6 $mg.kg^{-1}$ rocuronium bromide is used for rapid sequence induction of anesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.
For use of rocuronium bromide during rapid sequence induction of anesthesia in patients undergoing Cesarean section reference is made to section "Pregnancy and Lactation".

Maintenance dosing
The recommended maintenance dose is 0.15 $mg.kg^{-1}$ rocuronium bromide; in the case of long-term inhalational anesthesia, this should be reduced to 0.075-0.1 $mg.kg^{-1}$ 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 stimulations are present.

Continuous infusion
If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 $mg.kg^{-1}$ 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 stimulations. In adults under intravenous anesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6 $mg.kg^{-1}.h^{-1}$ and under inhalational anesthesia the infusion rate ranges from 0.3-0.4 $mg.kg^{-1}.h^{-1}$. Continuous monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anesthetic method used.

Pediatric patients
For infants (28 days-23 months), children (2-11 years) and adolescents (12-18 years) the recommended intubation dose during routine anesthesia and maintenance dose are similar to those in adults.
For continuous infusion in pediatrics, the infusion rates, with 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 stimulations 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 pediatric patients is limited. Rocuronium bromide is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in pediatric 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 during routine anesthesia is 0.6 $mg.kg^{-1}$ rocuronium bromide. A dose of 0.6 $mg.kg^{-1}$ should be considered for rapid sequence induction of anesthesia in patients in which a prolonged duration of action is expected. Regardless of the anesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 $mg.kg^{-1}$ rocuronium bromide, and the recommended infusion rate is 0.3-0.4 $mg.kg^{-1}.h^{-1}$ (see Continuous infusion). (See also section "Special Warnings and Precautions for Use").

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 $mg.kg^{-1}$ 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 stimulations. 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 $mg.kg^{-1}.h^{-1}$ 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 $mg.kg^{-1}.h^{-1}$ 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
Noveron is not recommended for the facilitation of mechanical ventilation in the intensive care in pediatric and geriatric patients due to a lack of data on safety and efficacy.

Administration
Noveron is administered intravenously either as a bolus injection or as a continuous infusion (see section "Instructions for Handling of the Product").

OVERDOSE
In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. Upon start of spontaneous recovery an acethylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of Noveron, ventilation must be continued until spontaneous breathing 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.

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 Noveron
Increased effect
- Halogenated volatile anesthetics potentiate the neuromuscular block of Noveron. The effect only becomes apparent with maintenance dosing (see section "Dosage and Administration"). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (see section "Special Warnings and Precautions for Use").
- Long-term concomitant use of corticosteroids and Noveron in the ICU may result in prolonged duration of neuromuscular block or myopathy (see sections "Special Warnings and Precautions for Use" and "Undesirable Effects").

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 ß-blocking agents.

Recurarization has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see section "Special Warnings and Precautions for Use").

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 Noveron 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 Noveron may produce potentiation or attenuation of the neuromuscular blocking effect of Noveron.

Effect of Noveron on other drugs
Noveron combined with lidocaine may result in a quicker onset of action of lidocaine.

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.

MedDRA SOC	Preferred term[a]		
	Uncommon/rare[b] (<1/100, >1/10 000)	Very rare (<1/10 000)	Not known
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock	
Nervous system disorders		Flaccid paralysis	
Eye disorders		Mydriasis[b,c] Fixed pupils[b,c]	
Cardiac disorders	Tachycardia		Kounis syndrome
Vascular disorders	Hypotension	Circulatory collapse and shock Flushing	
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Skin and subcutaneous tissue disorders		Angioneurotic edema Urticaria Rash Erythematous rash	
Musculoskeletal and connective tissue disorders		Muscular weakness[d] Steroid myopathy[d]	
General disorders and administration site conditions	Drug ineffective Drug effect/ therapeutic response decreased Drug effect/ therapeutic response increased Injection site pain Injection site reaction	Face oedema Malignant hyperthermia	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anesthesia	Airway complication of anesthesia	

[a] Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.
[b] Post-marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over three rather than five categories.

[c] In the context of a potential increase of permeability or compromise of the integrity of the Blood-Brain Barrier (BBB).
[d] after long-term use in the ICU

Anaphylaxis
Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Noveron, 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 non-depolarizing 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 "Special Warnings and Precautions for Use").

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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Appropriate Administration and Monitoring
Since Noveron 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.

Residual Curarization
As with other neuromuscular blocking agents, residual curarization has been reported for Noveron. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Geriatric patients (65 years or older) may be at increased risk for residual 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.

Anaphylaxis
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.

Long-Term Use in an Intensive Care Unit
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.

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

Risk of Death due to Medication Errors
Administration of Noveron results in paralysis, which may lead to respiratory arrest and death, a progression that may be more likely to occur in a patient for whom it is not intended. Confirm proper selection of intended product and avoid confusion with other injectable solutions that are present in critical care and other clinical settings. If another healthcare provider is administering the product, ensure that the intended dose is clearly labeled and communicated.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Noveron:
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, Noveron 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 Noveron may have profound effects and Noveron should be titrated to the response.

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

Obesity
Like other neuromuscular blocking agents, Noveron 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 Noveron
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.

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 Noveron to pregnant women.

Cesarean section
In patients undergoing Cesarean section, Noveron 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. Noveron, administered in doses of 0.6 $mg.kg^{-1}$, has been shown to be safe in parturients undergoing Cesarean section. Noveron 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 Noveron should be reduced and be titrated to twitch response.

Lactation
It is unknown whether Noveron is excreted in human breast milk. Animal studies have shown insignificant levels of Noveron in breast milk. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Noveron should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

INCOMPATIBILITIES
Physical incompatibility has been documented for Noveron when added to solutions containing the following drugs: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, frusemide, hydrocortisone sodium succinate, insulin, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. Noveron is also incompatible with Intralipid.
Noveron must not be mixed with other medicinal products except those mentioned in section "Instructions for Handling of the Product".
If Noveron is administered via the same infusion line that is also used for other drugs, it is important that this infusion line is adequately flushed (e.g. with 0.9% NaCl) between administration of Noveron and drugs for which incompatibility with Noveron has been demonstrated or for which compatibility with Noveron has not been established.

INSTRUCTIONS FOR HANDLING OF THE PRODUCT
Compatibility studies with the following infusion fluids have been performed: In nominal concentrations of 0.5 mg/mL and 2.0 mg/mL, Noveron has been shown to be compatible with: 0.9% NaCl, 5% dextrose, 5% dextrose in saline, sterile water for injections, Lactated Ringers. Administration should be begun immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

CONTRAINDICATION
Noveron is contraindicated in patients known to have hypersensitivity to rocuronium or to the bromide ion or to any of the excipients.

STORAGE
Intact vial of Noveron should be store between 2 - 8°C and protected from freezing. Intact vials stored below 30°C, should be used within 12 weeks. After first removal from the refrigerator, the 12 weeks shelf-life applies. The storage period may not exceed the labeled shelf-life.
After dilution with infusion fluids (see section '*Instruction for Handling of the Product*'), chemical and physical in-use stability has been demonstrated for 72 hours at 30°C. From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user/administrator and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

PRESENTATION
Box, 12 vials (clear borosilicate glass vial, with grey bromobutyl rubber stopper) @ 5 mL

ON MEDICAL PRESCRIPTION ONLY

Manufactured by :
NOVELL PHARMACEUTICAL LABORATORIES
Jl. Wanaherang No. 35, Tlajung Udik,
Gunung Putri, Bogor 16962, Indonesia

Pack. Code