SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Esmeron® 10 mg/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml Esmeron contains 10 mg rocuronium bromide.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
pH 3.8 – 4.2

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Esmeron is indicated in adult and pediatric patients (from term neonates to adolescents [0 to 18 years]) as an adjunct to general anesthesia to facilitate tracheal intubation during routine induction and to provide skeletal muscle relaxation during surgery. In adults, Esmeron is also indicated to facilitate tracheal intubation during rapid sequence induction and as an adjuvant in the Intensive Care Unit (ICU) to facilitate tracheal intubation and mechanical ventilation.

4.2 Posology and method of administration

Like other neuromuscular blocking agents, Esmeron should only be administered by, or under the supervision of, an experienced physician who is familiar with the action and use of these agents.

As with other neuromuscular blocking agents, the dosage of Esmeron should be individualized for each patient. The method of anesthesia and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, 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 of neuromuscular function.

Inhalational anesthetics potentiate the neuromuscular blocking effects of Esmeron. This potentiation only becomes clinically relevant during the course of the anesthesia, when the inhalational anesthetics have reached the tissue concentrations required for this interaction. Consequently, during lengthy procedures (lasting for longer than 1 hour) under inhalational anesthesia, lower maintenance doses of Esmeron should be administered at less frequent intervals or the infusion rates should be reduced (see section 4.5).

In adults, the following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for short to lengthy surgical procedures and for use in the ICU.

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} rocuronium bromide is recommended for facilitating tracheal intubation during rapid sequence induction of anesthesia, after which adequate intubation conditions are also 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.

Cesarean section
Doses of 0.6 mg.kg^{-1} rocuronium bromide do not affect the Apgar score, fetal 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 clinical adverse effects in the newborn.

Doses of 1.0 mg.kg^{-1} have been investigated during rapid sequence induction of anesthesia, but not in patients undergoing Cesarean section.

Higher doses
Should there be a reason for selecting a higher dose: initial doses up to 2 mg.kg^{-1} rocuronium bromide have been administered to patients without adverse cardiovascular effects being noted. Use of a higher dose decreases the onset time and increases the duration of action (see section 5.1).

Maintenance dose
The recommended maintenance dose is 0.15 mg.kg^{-1} rocuronium bromide; in the case of prolonged 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 TOF-stimulation (train of four) 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. When neuromuscular function starts to recover, administration by continuous infusion can be started. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 to 2 responses to TOF stimulation. In adults under intravenous anesthesia, this corresponds to an infusion rate of 0.3-0.6 mg.kg^{-1}.h^{-1}, and under inhalational anesthesia to an infusion rate of 0.3-0.4 mg.kg^{-1}.h^{-1}. Continuous monitoring of neuromuscular block is recommended, since the required dosage varies from patient to patient and depends on the anesthetic method used.

Pediatric patients
For neonates (0-27 days), infants (28 days-2 months), toddlers (3-23 months), children (2-11 years) and adolescents (12-17 years), the recommended intubation dose during routine anesthesia and maintenance dose are similar to those in adults.
However, the duration of action of the single intubating dose will be longer in neonates and infants than in children (see section 5.1).

For continuous infusion in pediatric patients, the infusion rates, with the exception of children (2-11 years), are the same as for adults. For children aged 2-11 years, higher infusion rates might be necessary.

Thus, for children (2-11 years), the same initial dosage as for adults is recommended; this should then be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to TOF-stimulation during the procedure.

Experience with rocuronium bromide during 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 disorders and/or renal failure
The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disorders 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 whom 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' and also section 4.4).

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 and calculated on the basis of ideal body weight.

Use in Intensive Care

Tracheal intubation
For tracheal intubation, the dose recommendations are the same as for surgical procedures.

Maintenance dose
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 TOF-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^{-1}.h^{-1} during the first hours of administration. The infusion rate should be decreased during the following 6 - 12 hours, according to the individual response. Thereafter, dose requirements remain relatively constant.

A high variability in infusion rates was seen in clinical studies. The mean infusion rate ranged from 0.2-0.5 mg.kg^{-1}.h^{-1} depending on the nature and extent of organ failure, concomitant medication and the condition of the individual patient. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Administration for up to 7 days has been investigated.

Special populations
Esmeron is not recommended for the facilitation of mechanical ventilation in pediatric and geriatric patients due to a lack of data on safety and efficacy.

Administration

Esmeron is administered intravenously either as a bolus injection or as a continuous infusion (see section 6.6).

4.3 Contraindications

Hypersensitivity to rocuronium or the bromide ion or to any of the excipients listed in section 6.1.

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. In the case of intubation difficulties resulting in a clinical need for immediate reversal of a rocuronium bromide-induced neuromuscular block, the use of sugammadex should be considered.

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. 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 the condition of the patient) should also be considered. If it is not standard clinical practice, the use of sugammadex or another reversal agent (for example, an acetylcholinesterase inhibitor) 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. In particular, extreme caution should be exercised in the case of previous anaphylactic reactions to neuromuscular blocking agents, since allergic cross-reactivity to neuromuscular blocking agents has been reported. 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 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.

In general, following long-term use of muscle relaxants 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 block is monitored throughout the use of muscle relaxants. In addition, it is essential that patients receive adequate analgesia and sedation during neuromuscular block. Furthermore, doses should be titrated to effect in the individual patients by, or under the supervision of, an experienced physician who is familiar with the actions of neuromuscular blocking agents and with appropriate neuromuscular monitoring techniques.

Myopathy has been reported frequently after long-term administration of other non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of neuromuscular blocking agents should be limited as much as possible.

If suxamethonium is used for intubation, it is recommended to delay the administration of rocuronium bromide until the patient has recovered from the neuromuscular block induced by suxamethonium.

Because rocuronium bromide is always used with other drugs and because of the risk of malignant hyperthermia during anesthesia, even in the absence of known triggering factors, physicians should be aware of the early symptoms, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of anesthesia. Animal studies have shown that rocuronium bromide is not a triggering factor for malignant hyperthermia. Rare cases of malignant hyperthermia with Esmeron have been observed thru post-marketing surveillance; however, the causual association has not been proven.
The following conditions may influence the pharmacokinetics and/or pharmacodynamics of rocuronium bromide:

Hepatic and/or biliary tract disorders 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 disease 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 an edematous 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 reduced plasma clearance.

Neuromuscular disease
As with 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 altered considerably in these cases. The magnitude and the nature 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 response.

Hypothermia
When surgery is performed under hypothermic conditions, the neuromuscular blocking effect of rocuronium bromide is increased and the duration of action is prolonged.

Obesity
Like other neuromuscular blocking agents, rocuronium bromide may exhibit a prolonged duration of action and a prolonged spontaneous recovery time in obese patients when the administered doses are calculated on the basis of 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.

Treatment with magnesium salts for toxemia of pregnancy
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. The dosage of rocuronium bromide in these patients should be reduced and titrated on the basis of twitch response.

Conditions which may increase the effects of rocuronium bromide
Hypokalemia (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, before administration of rocuronium bromide.

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.

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 anticholinesterase inhibitors could also be inhibited
- after intubation with suxamethonium (see section 4.4)
- long-term use of corticosteroids and rocuronium bromide in the ICU may result in a prolonged duration of neuromuscular block or myopathy (see sections 4.4 and 4.8)

Other drugs
- antibiotics: aminoglycoside and polypeptide antibiotics, lincosamide and 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 4.4).

Decreased effect
- prior chronic administration of corticosteroids, 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.

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

Pediatric 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 pediatric patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no clinical data on the use of rocuronium bromide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3). Caution should be exercised when administering 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 suxamethonium is used during intubation. Rocuronium bromide, administered in doses of 0.6 mg.kg^{-1}, has been shown to be safe for use during Cesarean section. Rocuronium bromide does not affect Apgar score, fetal 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.

N.B.:
- 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.
- 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 breast milk. Other medicinal products of the same class demonstrate limited secretion in breast milk and low resorption by the infant. Insignificant levels of rocuronium bromide were found in the milk of lactating rats. Rocuronium bromide should only be given to women who are breastfeeding when the attending physician decides that the benefits outweigh the risks. After the administration of a single dose, it is recommended to abstain from next breastfeeding for five elimination half-lives of rocuronium, i.e. for about 6 hours.

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

Summary of the safety profile
The most common adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reaction during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms. See also the explanations below the table.

Tabulated list of adverse reactions

MedDRA System organ class	MedDRA preferred term[1]		
	Uncommon/rare[2] (<1/100, >1/10,000)	Very rare[2] (<1/10,000)	Not Known
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock	
Nervous system disorders		Flaccid paralysis	
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[3] Steroid myopathy[3]	
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 edema	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anesthesia	Airway complication of anesthesia	

[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 three rather than five categories.
[3] After long-term use in the Intensive Care.

Class effects
Anaphylactic reactions
Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including rocuronium bromide, have been reported. Anaphylactic/anaphylactoid reactions include symptoms such as bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia and circulatory collapse/shock) and cutaneous changes (e.g. angioedema and urticaria). These reactions have been fatal in some cases. Due to the possible severity of these reactions, one should always assume they may occur and take the necessary precautions (see also section 4.4).

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.
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 neuromuscular blocking agents as a class consists of prolongation 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 also sections 4.4 and 4.5).

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.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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) 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 at the correct dose. When administration of an acetylcholinesterase inhibitor fails to reverse the neuromuscular effects of rocuronium bromide, ventilation must be continued until spontaneous breathing is restored. Repeated administration of an acetylcholinesterase inhibitor can be dangerous.

In animal studies, severe depression of cardiovascular function, eventually leading to cardiac failure, did not occur until a cumulative dose of 750 x ED_{90} (135 mg rocuronium bromide per kg body weight) was administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code)
Muscle relaxants, peripherally acting agents. ATC code: M03A C09

Mechanism of action
Esmeron (rocuronium bromide) is a fast-onset, non-depolarizing neuromuscular blocking agent which has all of the pharmacological properties characteristic of this class of drugs (curariform). It acts by competitive blockade of nicotinic cholinoceptors at the motor endplate. This action is antagonized by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

Pharmacodynamic effects
The ED_{90} (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during intravenous anesthesia is approximately 0.3 mg.kg^{-1} rocuronium bromide. The ED_{95} in neonates and infants is lower than in adults and children (0.25, 0.35 and 0.40 mg.kg^{-1}, respectively).

The clinical duration of action (the time between administration and recovery to 25% of control twitch height) at a dose of 0.6 mg.kg^{-1} rocuronium bromide is 30-40 minutes. The total duration of action (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% after a bolus dose of 0.6 mg.kg^{-1} rocuronium bromide is 14 minutes. With lower doses of 0.3-0.45 mg.kg^{-1} rocuronium bromide (1-1.5 x ED_{90}), onset of action is slower and duration of action is shorter. With a higher dose of 2 mg.kg^{-1}, the duration of action is 110 minutes.

Intubation during routine anesthesia
Within 60 seconds following intravenous administration of a dose of 0.6 mg.kg^{-1} rocuronium bromide (2x ED_{90} under intravenous anesthesia), adequate intubation conditions can be achieved in nearly all patients, of which in 80% intubation conditions are rated as excellent.
General muscle paralysis adequate for any type of procedure is established within 2 minutes after administration of this dose. After administration of 0.45 mg.kg^{-1} rocuronium bromide, acceptable intubation conditions are achieved after 90 seconds.

Rapid sequence induction
During rapid sequence induction of anesthesia with propofol or fentanyl/thiopental, adequate intubation conditions are achieved within 60 seconds in 93% and 96% of the patients respectively, following a dose of 1.0 mg.kg^{-1} rocuronium bromide. In these groups, in 70% of the cases the intubation conditions are rated as excellent. The clinical duration of action with this dose approaches 1 hour, after which the neuromuscular block can be safely reversed. Following a dose of 0.6 mg.kg^{-1} 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 and fentanyl/thiopental, respectively.

Pediatric population
Mean onset time in infants, toddlers and children at an intubation dose of 0.6 mg.kg^{-1} is slightly shorter than in adults. Comparisons between the pediatric age groups showed that the mean onset time in neonates and adolescents (1.0 min.) is slightly longer than in infants, toddlers and children (0.4, 0.6 and 0.8 min., respectively). The duration of action and the time to recovery tend to be shorter in children compared to infants and adults.
Comparisons between the pediatric age groups demonstrated that the mean time to reappearance of T_3 was prolonged in neonates and infants (56.7 and 60.7 min., respectively) in comparison with toddlers, children and adolescents (45.5, 37.6 and 42.9 min., respectively).

Mean (SD) time to onset and clinical duration of action following an initial intubating dose* of 0.6 mg/kg rocuronium bromide during sevoflurane/nitrous oxide and isoflurane/nitrous oxide (maintenance) anesthesia (pediatric patients)

	Time to maximum block** (min)	Time to reappearance of T_3** (min)
Neonates (0-27 days) n=10	0.98 (0.62)	56.69 (37.04) n=9
Infants (28 days-2 months) n=11	0.44 (0.19) n=10	60.71 (16.52)
Toddlers (3-23 months) n=28	0.59 (0.27)	45.46 (12.94) n=27
Children (2-11 years) n=34	0.84 (0.29)	37.58 (11.82)
Adolescents (12-17 years) n=31	0.98 (0.38)	42.90 (15.83) n=30

* Dose of rocuronium bromide administered within 5 seconds.
** Calculated from the end of administration of the rocuronium bromide intubating dose.

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure
The duration of action of maintenance doses of 0.15 mg.kg^{-1} rocuronium bromide might be somewhat longer under enflurane and isoflurane anesthesia in geriatric patients and in patients with hepatic disease and/or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous anesthesia (approximately 13 minutes) (see section 4.2). No accumulation of effect (progressive increase in duration of action) has been observed with repeated maintenance doses at the recommended level.

ICU
Following prolonged continuous infusion in the ICU, the time to recovery of the TOF-ratio to 0.7 depends on the level of neuromuscular block at the end of the infusion. After continuous infusion for 20 hours or more, the median time between return of T_2 to TOF-stimulation and recovery of the TOF-ratio to 0.7 is approximately 1.5 (range 1-5) hours in patients without multiple organ failure and 4 (range 1-25) hours in patients with multiple organ failure.

Cardiovascular surgery
In patients undergoing cardiovascular surgery, the most common cardiovascular changes during the onset of maximum block following 0.6-0.9 mg.kg^{-1} 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
The action of rocuronium bromide can be antagonized either by sugammadex or by acetylcholinesterase inhibitors (neostigmine, pyridostigmine or edrophonium). Sugammadex can be given for routine reversal (at 1-2 post-tetanic counts up to reappearance of T_2) or for immediate reversal (3 minutes after rocuronium bromide administration). Acetylcholinesterase inhibitors can be administered at reappearance of T_2 or at the first signs of clinical recovery.

5.2 Pharmacokinetic properties

After intravenous administration of a single bolus dose of rocuronium bromide, the plasma concentration time course runs in three exponential phases. In adults, the mean elimination half-life is 73 (95% CI: 66-80) minutes, the (apparent) volume of distribution under steady-state conditions is 203 (193-214) ml.kg^{-1} and plasma clearance is 3.7 (3.5-3.9) ml.kg^{-1}.min^{-1}.

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 feces after 9 days. Approximately 50% is recovered as unchanged rocuronium.

Pediatric patients
The pharmacokinetics of rocuronium bromide in pediatric patients (n=146) with ages ranging from 0 to 17 years were evaluated using a population analysis of the pooled pharmacokinetic datasets from two clinical trials in which anesthesia was induced with sevoflurane and maintained with isoflurane/nitrous oxide. All pharmacokinetic parameters were found to be linearly proportional to body weight, illustrated by a similar clearance (l.hr^{-1}.kg^{-1}). The volume of distribution (l.kg^{-1}) and elimination half-life (h) decrease with age (years). The pharmacokinetic parameters of typical pediatric patients within each age group are summarized below:

Estimated PK parameters (mean [SD]) of rocuronium bromide in typical pediatric patients during sevoflurane and nitrous oxide (induction) and isoflurane/nitrous oxide (maintenance anesthesia)

PK parameters	Patient age range				
	Term newborn infants (0-27 days)	Infants (28 days -2 months)	Toddlers (3-23 months)	Children (2-11 years)	Adolescents (12-17 years)
Cl (l/kg/hr)	0.31 (0.07)	0.30 (0.08)	0.33 (0.10)	0.35 (0.09)	0.29 (0.14)
Volume of distribution (l/kg)	0.42 (0.06)	0.31 (0.03)	0.23 (0.03)	0.18 (0.02)	0.18 (0.01)
$t_{½}\beta$ (hr)	1.1 (0.2)	0.9 (0.3)	0.8 (0.2)	0.7 (0.2)	0.8 (0.3)

Geriatric patients and patients with hepatic and/or biliary tract disorders and/or renal failure
In controlled studies the plasma clearance in geriatric patients and in patients with renal failure was reduced. In most studies, however, this did not reach the level of statistical significance. In patients with hepatic failure, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 ml.kg^{-1}.min^{-1} (see section 4.2).

Intensive Care
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 interindividual variability was found in controlled clinical studies, related to the nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure, the mean (± SD) elimination half-life is 21.5 (± 3.3) hours, the (apparent) volume of distribution at steady state is 1.5 (± 0.8) l.kg^{-1} and the plasma clearance is 2.1 (± 0.8) ml.kg^{-1}.min^{-1}.

5.3 Preclinical safety data

Effects in animal studies were observed only at exposures sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

There is no proper animal model to mimic the usually extremely complex clinical situation of the ICU patient. Therefore, the safety of Esmeron when used to facilitate mechanical ventilation in the ICU has primarily been assessed on the basis of the results obtained in clinical studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Esmeron contains the following excipients:
- sodium acetate (for pH adjustment)
- sodium chloride
- acetic acid (for pH adjustment)
- water for injection.

6.2 Incompatibilities

Physical incompatibility has been documented for Esmeron when added to solutions containing the following drugs: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. Esmeron is also incompatible with Intralipid.

This medicinal product must not be mixed with other medicinal products other than those mentioned in section 6.6.

If Esmeron 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 Esmeron and drugs for which incompatibility with Esmeron has been demonstrated or for which compatibility with Esmeron has not been established.

6.3 Shelf life

3 years

Esmeron does not contain a preservative; the solution should be used immediately after opening the vial.

The chemical and physical in-use stability of the diluted product (see section 6.6) has been demonstrated for 72 hours at 30°C. From a microbiological point of view, the product should be used immediately after dilution. 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 the dilution method rules out microbiological contamination.

6.4 Special precautions for storage

Store in the refrigerator (2-8°C).

The product can be stored outside the refrigerator at a temperature of up to 30°C for a maximum of 12 weeks. Once it has been kept outside the refrigerator, the product may not be placed back. The storage period may not exceed the shelf life.

6.5 Nature and contents of container

Glass vial, rubber stopper and aluminum crimp cap with plastic cap.
The rubber stopper of the vial does not contain latex.

There are 3 presentations of Esmeron:
- Packaging of 10 vials of 2.5 ml each containing 25 mg rocuronium bromide.
- Packaging of 10 vials of 5 ml each containing 50 mg rocuronium bromide.
- Packaging of 10 vials of 10 ml each containing 100 mg rocuronium bromide.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Compatibility studies have been performed with the following infusion fluids. In nominal concentrations of 0.5 mg/ml and 2.0 mg/ml, Esmeron has been shown to be compatible with: 0.9% NaCl, 5% dextrose, 5% dextrose in 0.9% NaCl, sterile water for injections, lactated Ringers and Haemaccel. Administration should be started immediately after mixing, and should be completed within 24 hours. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER, BATCH RELEASING SITE & MANUFACTURER

MARKETING AUTHORISATION HOLDER & BATCH RELEASING SITE

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

MANUFACTURER

Siegfried Hameln GmbH
Langes Feld 13,
31789 Hameln,
Germany

8. DATE OF REVISION OF THE TEXT

March 2020

THIS IS A MEDICAMENT
• Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
• Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
• The doctor and the pharmacist are the experts in medicines, their benefits and risks.
• Do not by yourself interrupt the period of treatment prescribed.
• Do not repeat the same prescription without consulting your doctor.
• Keep all medicaments out of reach of children.
Council of Arab Health Ministers & Union of Arab Pharmacists