## 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 a 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 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. Esmeron 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.

### 4.2 Posology and method of administration

Like other neuromuscular blocking agents, Esmeron 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 Esmeron 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 Esmeron. 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 Esmeron should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Esmeron during long lasting procedures (longer than 1 hour) under inhalational anesthesia (see section 4.5).

**Risk of Medication Errors:** Accidental administration of neuromuscular blocking agents may result in serious adverse events, including fatal outcomes. Store Esmeron with the cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product (see section 4.4).

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 4.6.

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 stimulation are present.

Continuous infusion

If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 $mg.kg^{-1}$ 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 stimulation. 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 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 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 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 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 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 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

Esmeron 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

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 to the bromide ion or to any of the excipients.

## 4.4 Special warnings and precautions for use

### Appropriate Administration and Monitoring

Since Esmeron 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 Esmeron. 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 Esmeron 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 Esmeron 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 labelled and communicated.

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

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, Esmeron 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 Esmeron may have profound effects and Esmeron should be titrated to the response.

Hypothermia

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

Obesity

Like other neuromuscular blocking agents, Esmeron 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 Esmeron

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

Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

### Effect of other drugs on Esmeron

Increased effect

- Halogenated volatile anesthetics potentiate the neuromuscular block of Esmeron. The effect only becomes apparent with maintenance dosing (see section 4.2). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (see section 4.4).
- Long-term concomitant use of corticosteroids and Esmeron in the ICU may result in prolonged duration of neuromuscular block or myopathy (see sections 4.4 and 4.8).

Other drugs

- antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.
- diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anesthetics (lidocaine i.v,

bupivacaine epidural) and acute administration of phenytoin or 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 phenytoin or carbamazepine.
- Protease inhibitors (gabexate, ulinastatin).

Variable effect

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

**Effect of Esmeron on other drugs**

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

## 4.6 Pregnancy and lactation

Pregnancy

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

Cesarean section

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

Lactation

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

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

| MedDRA SOC | Preferred term[a] | | |
|---|---|---|---|
| | Uncommon/rare[b] (<1/100, >1/10 000) | Very rare (<1/10 000) | Not known |
| Immune system disorders | | Hypersensitivity<br>Anaphylactic reaction<br>Anaphylactoid reaction<br>Anaphylactic shock<br>Anaphylactoid shock | |
| Nervous system disorders | | Flaccid paralysis | |
| Eye disorders | | Mydriasis[b,c]<br>Fixed pupils[b,c] | |
| Cardiac disorders | Tachycardia | | Kounis syndrome |
| Vascular disorders | Hypotension | Circulatory collapse and | |

[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).

| | | | |
|---|---|---|---|
| | | shock<br>Flushing | |
| Respiratory, thoracic and mediastinal disorders | | Bronchospasm | |
| Skin and subcutaneous tissue disorders | | Angioneurotic edema<br>Urticaria<br>Rash<br>Erythematous rash | |
| Musculoskeletal and connective tissue disorders | | Muscular weakness[d]<br>Steroid myopathy[d] | |
| General disorders and administration site conditions | Drug ineffective<br>Drug effect/ therapeutic response decreased<br>Drug effect/ therapeutic response increased<br>Injection site pain<br>Injection site reaction | Face oedema<br>Malignant hyperthermia | |
| Injury, poisoning and procedural complications | Prolonged neuromuscular block<br>Delayed recovery from anesthesia | Airway complication of anesthesia | |

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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.

[d] after long-term use in the ICU

angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume they may occur and take the necessary precautions.

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

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

Prolonged neuromuscular block

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Myopathy

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

Local injection site reactions

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

than 0.5% of the patients who underwent rapid sequence induction of anesthesia with fentanyl and thiopental.

## 4.9 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 acetylcholinesterase 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 Esmeron, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code)

Muscle relaxants, peripherally acting agents. ATC code: M03AC09

Mechanism of action

Esmeron (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.

Pharmacodynamic effects

The ED90 (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 ED95 in infants is lower than in adults and children (0.25, 0.35 and 0.40 $mg.kg^{-1}$, respectively).

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with 0.6 $mg.kg^{-1}$ 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 $mg.kg^{-1}$ rocuronium bromide is 14 minutes. With lower dosages of 0.3-0.45 $mg.kg^{-1}$ rocuronium bromide (1-1½ x ED90), onset of action is slower and duration of action is shorter.

Should there be reason for selection of larger doses in individual patients, initial doses up to 2 $mg.kg^{-1}$ rocuronium bromide have been administered during surgery without adverse cardiovascular effects being noted. The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of action. With high doses of 2 $mg.kg^{-1}$, clinical duration 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 ED90 under intravenous anesthesia), 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 $mg.kg^{-1}$ rocuronium bromide, acceptable intubation conditions are present after 90 seconds.

Rapid Sequence Induction

During rapid sequence induction of anesthesia under propofol or fentanyl/thiopental anesthesia, 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. 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 $mg.kg^{-1}$ 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 or fentanyl/thiopental, respectively.

Special populations

Mean onset time in infants and children at an intubation dose of 0.6 $mg.kg^{-1}$ 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 $mg.kg^{-1}$ 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) 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 $T_2$ 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$^{-1}$ Esmeron 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 $T_2$ or at the first signs of clinical recovery, antagonizes the action of Esmeron.

## 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 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$^{-1}$ and plasma clearance is 3.7 (3.5-3.9) ml.kg$^{-1}$.min$^{-1}$.

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 with 30 minutes and the mean plasma clearance is reduced by 1 ml.kg$^{-1}$.min$^{-1}$. (See section 4.2.)

In infants (3 months to 1 yr), the apparent volume of distribution at steady state conditions is increased compared to adults and children (1-8 yr). 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) $l.kg^{-1}$ and a plasma clearance of 2.1 (± 0.8) $ml.kg^{-1}.min^{-1}$ 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 feces after 9 days. Approximately 50% is recovered as the parent compound.

### 5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered 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 Intensive Care Unit is mainly based on 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

No preservative has been added.

## 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, frusemide, hydrocortisone sodium succinate, insulin, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. Esmeron is also incompatible with Intralipid.

Esmeron must not be mixed with other medicinal products except 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

Esmeron has a shelf life of 3 years, provided it is stored under the prescribed conditions (see Special precautions for storage). The date mentioned on the carton and on the label of the vial is the expiry date; this is the date up to which Esmeron may be used. Since Esmeron does not contain a preservative, the solution should be used immediately after opening the vial.

After dilution with infusion fluids (see section 6.6), 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.

## 6.4 Special precautions for storage

Store in the refrigerator at 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. After first removal from the refrigerator, the 12 week shelf life applies. The storage period may not exceed the labeled shelf life.

## 6.5 Nature and contents of container

Esmeron 25 mg=2.5 ml

Packaging of 10 vials each containing 25 mg rocuronium bromide.

Esmeron 50 mg=5 ml

Packaging of 10 vials each containing 50 mg rocuronium bromide.

Esmeron 100 mg=10 ml

Packaging of 10 vials each containing 100 mg rocuronium bromide.

Not all pack sizes may be marketed.

The rubber stopper of the vial does not contain latex.

In correspondence please quote packaging number.

## 6.6 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 Esmeron has been shown to be compatible with: 0.9% NaCl, 5% dextrose, 5% dextrose in saline, sterile water for injections, Lactated Ringers and Haemaccel. Administration should be begun immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

## 7. DATE OF REVISION OF THE TEXT

June 2022

## 8. PRODUCT OWNER

Merck Sharp & Dohme LLC
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Rahway, New Jersey 07065
USA

MSD