

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 T₃ 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 T₂ 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 T₂) or for immediate reversal (3 minutes after rocuronium bromide administration). Acetylcholinesterase inhibitors can be administered at reappearance of T₂ 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 _{1/2} β (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 Haemacel. 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

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The Netherlands

MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

March 2020

<p>THIS IS A MEDICAMENT</p> <ul style="list-style-type: none"> 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. <p>Council of Arab Health Ministers & Union of Arab Pharmacists</p>
