SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

MYOCRON 50mg/5ml I.V. Solution for Injection, Vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each 1 ml of MYOCRON contains 10 mg rocuronium bromide.

Excipient(s):

Sodium acetate	2 mg/ml
Sodium chloride	3.3 mg/ml

For full list of excipients, see 6.1

3. PHARMACEUTICAL FORM

Solution for injection, vial.

Clear, colorless solution, pH:3.8-4.2

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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 rocuronium bromide, after which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0 mg/kg rocuronium bromide is recommended for facilitating tracheal intubation conditions during rapid sequence induction of an anesthesia, after which adequate intubation conditions are established within 60 seconds in nearly all patients. If a dose of 0.6 mg/kg rocuronium bromide is used for rapid sequence induction of anesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

Use of rocuronium bromide during rapid sequential induction of anesthesia in patients with caesarean is discussed in Section 4.6.

Higher doses

Rocuronium bromide up to 2 mg / kg was administered as an initial dose at the time of surgery without adverse (reverse) cardiovascular effects when there was a reason to require higher doses in patients individually. The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of effect. (See Section 5.1)

Maintenance dosage

The recommended maintenance dose is 0.15 mg/kg rocuronium bromide; in the case of long-term inhalational anesthesia this should be reduced to 0.075-0.1 mg/kg rocuronium bromide.

The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height, or when 2 to 3 responses to train of four 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 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/h (300-600 micrograms/kg/h) and under inhalational anesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anesthetic method used.

Information on special populations:

Pediatric patients

For newborn babies (0-27 days), infants (28 days-2 months), nursling children (3-23 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.

However, the duration of the single intubation dose action is longer in newborns and infants than in children (see section 5.1).

For continuous infusion in pediatrics, the infusion rates with the exception of children (aged 2-11) are the same as for adults. Faster infusion rates may be needed for children. 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 infants (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.

Dose in 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 rocuronium bromide. A dose of 0.6 mg/kg should be preferred 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 rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg/kg/h (see also 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 dosage

The use of an initial loading dose of 0.6 mg/kg rocuronium bromide is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train of four stimulations. Dosage should always be titrated according to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80-90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3-0.6 mg/kg/h during the first hour of administration, which will need to be decreased during the following 6-12 hours, according to the individual response. Thereafter, individual dose requirements remain relatively constant.

A large variability between patients in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2-0.5 mg/kg/h depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Administration up to 7 days has been investigated.

Additional information on special populations

It 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.

Method of administration

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

Special populations:

Kidney and liver failure:

Since rocuronium passes through bile and urea, it should be used with caution in patients with clinically significant liver and kidney disease and / or insufficiency. Prolonged action with rocuronium bromide dosing of 0.6 mg / kg was observed in these patient groups.

Pediatric population:

Pediatric patients are not advised to provide mechanical ventilation in the intensive care unit because of insufficient data on safety and efficacy.

Geriatric population:

In geriatric patients, mechanical ventilation in the intensive care unit is not recommended due to insufficient data on safety and efficacy for ensuring ventilation.

4.3 Contraindications

Hypersensitivity to rocuronium or bromide ion or any of the excipients

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 active substance until adequate spontaneous respiration is restored.

As with all neuromuscular blocking agents, it should be anticipated intubation difficulties, particularly when used as part of a rapid sequence induction technique.

As with other neuromuscular blocking agents, residual curarization has been reported for Rocuronium. Elderly patients (aged 65 years and over) may be at increased risk for residual neuromuscular block. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Other factors which could cause residual curarization after extubation in the post-operative phase (such as drug interactions or patient conditions) 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.

Anaphylactic reactions can occur after the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross-reactivity to neuromuscular blocking agents has been reported.

Rocuronium may increase heart beat rate.

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 blockage and/or overdose, it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to the effect in the individual patient. This should be performed by or under the supervision of experienced clinicians who are familiar with the effects and with appropriate neuromuscular monitoring techniques.

Myopathy has been reported after long-term concurrent use of non-depolarizer neuromuscular blockers and corticosteroids. Therefore, both for patients administered neuromuscular blockers and corticosteroids, the use period of neuromuscular blockers should be as short as possible.

If suxamethonium is used for intubation, the application of MYOCRON should be delayed until the patient is clinically awakened from the neuromuscular block induced by suxamethonium.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of MYOCRON.

Hepatic and/or biliary tract disease and renal failure

Rocuronium bromide is excreted in urine and bile. Therefore, 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 the effect has been observed with doses of 0.6 mg/kg.

Prolonged circulation time

Conditions associated with prolonged circulation time such as cardiovascular diseases, old age and increase in dispersion time, may contribute to a slower onset of the effect. The duration of action may also be prolonged due to reduced plasma cholinesterase.

Neuromuscular disease

Like other neuromuscular blocking agents, MYOCRON should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenia (Eaton-Lambert) syndrome, small doses of MYOCRON may have profound effects and MYOCRON should be titrated to effect dose.

Hypothermia

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

Obesity

Like other neuromuscular blocking agents, MYOCRON 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 the response.

Conditions which may increase the effects of MYOCRON

Hypokalaemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnia and cachexia

Therefore, severe electrolyte disturbances, altered blood pH or dehydration should be corrected when possible.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose; no side effects due to sodium are expected at this dose.

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.

Effects of other drugs on MYOCRON;

Increasing effect:

- Halogenated volatile anesthetic agents are intensified to neuromuscular block of MYOCRON. Effect only becomes clear with maintenance dosage (See Section 4.2). Returning block can be prevented with inhibitor of anticholinesterase.
- After intubation with suxamethonium (see section 4.4).

- Usage of corticosteroids and MYOCRON in intensive care unit can be caused to neuromuscular block or myopathy (See Section 4.4 and 4.8).

Other drugs:
- Antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino penicillin antibiotics,
- Diuretics, kinidin and its isomer of kinin, magnesium salts, agents of blocking calcium canal, lithium salts, local anesthetics (lidocaine intravenous, bupivacaine epidural), bolus administration of phenytoin or β-blocking agents.

Recurrence was reported with administration of aminoglycoside, lincosamide, polypeptide and acylamino penicillin antibiotics, kinidin, kinin and magnesium salts after surgery (see section 4.4).

Decreasing effect:
- Before chronic administration of phenytoin or carbamazepine.
- Calcium chloride, potassium chloride
- Inhibitor of protease (gabexate, ulinastatin)

Changeable effect:
- Neuromuscular block can be get stronger or weaken because of the combination administration MYOCRON and other non- depolarizing neuromuscular blocking agents, depending on administration and type of neuromuscular blocking agents.
- Administration of succinylcholine after MYOCRON can be caused to get stronger or weaken to effects of neuromuscular blocking of MYOCRON.

Effects of MYOCRON on other drugs:

MYOCRON can be caused to faster beginning of lidocaine's effect as combined with Lidocaine.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: C

Women with childbearing potential / birth control (contraception)

During treatment with rocuronium, it is recommended that women with childbearing potential should use effective contraceptive methods

Pregnancy

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

Caesarean section

In patients undergoing Caesarean 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 following suxamethonium facilitated intubation. The rocuronium bromide administered at doses of 0.6 mg / kg has shown not to provide appropriate condition up to 90 seconds for proper intubation. Rocuronium bromide administered at doses of 0.6 mg / kg has been shown to be safe in pregnant women with cesarean section.

Rocuronium bromide does not adversely 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.

Note 1: Doses of 1.0 mg/kg have been investigated during rapid sequence induction of anesthesia, but not in caesarean section patients. Therefore, only a dose of 0.6 mg/kg is recommended in this patient group.

Note 2: Reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of MYOCRON should be reduced and be titrated to level of twitch response.

Lactation

It is unknown whether MYOCRON are excreted in human milk or not. Animal studies have shown excretion of rocuronium bromide in insignificant amounts in breast milk.

In animal studies; pregnancy, embryonal / fetal development, birth or postpartum development, direct or indirect harmful effects have not been indicated. MYOCRON should

only be applied to breastfeeding women if the responsible doctor believes that the benefit to be obtained will be more than the risk.

Reproduction ability / Fertility

No studies with animals have been performed to assess the carcinogenic potential or fertility of rocuronium bromide.

4.7 Effects on ability to drive and use machines

Since MYOCRON 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 in the table below.

The undesirable effects are listed below according to the system organ class. The frequencies are defined as follows:

In different organ systems;

Very common (≥ 1/10),

Common (≥ 1/100 to < 1/10),

Uncommon (≥ 1/1,000 to <1/100),

Rare (≥ 1/10.000 to <1/1.000),

Very rare (<1/10.000),

Unknown (cannot be estimated from the available data).

MedDRA SOC	Preferred term[a]	
	Uncommon(≥ 1/1.000 to ≤ 1/100) /rare (≥ 1/10.000 to ≤	Very rare (<1/10 000)

	l/1.000)[b]	
Immune system disorders		Hypersensitivity
		Anaphylactic reaction
		Anaphylactoid reaction
		Anaphylactic shock
		Anaphylactoid shock
Nervous system disorders		Flaccid paralysis
Cardiac disorders	Tachycardia	
Vascular disorders	Hypotension	Circulatory collapse and shock Hot flush
Respiratory, thoracic and mediastinal disorders		Bronchospasm
Skin and subcutaneous tissue disorders		Angioneurotic edema
		Urticaria
		Erythematous rash
		Red rash
Musculoskeletal and connective tissue disorders		Muscular weakness[c]
		Steroid myopathy[c]
General disorders and administration site conditions	Drug ineffective	Face edema Malignant hyperthermia
	Drug effect/ therapeutic response decreased	
	Drug effect/ therapeutic response increased	
	Injection site pain	
	Injection site reaction	
Injury, poisoning and procedural complications	Prolonged neuromuscular block	Airway complication of anesthesia
	Delayed recovery from anesthesia	

[1] Frequencies are estimated derived from post-marketing surveillance reports and data from the general literature.

[2] Post-marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over two rather than five categories.

[3] After long-term use in the ICU

Anaphylaxis

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including rocuronium bromide, have been reported.

Anaphylactic/anaphylactoid reaction: bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse – shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions are fatal in some cases. 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 reaction 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 rocuronium bromide.

Prolonged neuromuscular block

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

Myopathy

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

Local injection site reactions

During rapid sequence induction of anesthesia, pain on injection site 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 0.5% of the patients who underwent rapid sequence induction of anesthesia with fentanyl and thiopental.

Pediatric patients

In a meta-analysis of 11 clinical trials conducted with rocuronium bromide (1 mg / kg) in pediatric patients (n = 704), tachycardia was identified as adverse effect at a frequency of 1.4%.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-posta: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99).

4.9 Overdose and Treatment

In the event of overdose and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. Nöromüsküler bloğu tersine çevirmek için iki seçenek vardır: (1) sugammadeks in adults can be used to reverse sharp and deep blisters. The sugammadex dose to be administered depends on the level of neuromuscular block. (2) Upon start of spontaneous recovery an acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) or sugammadex should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of MYOCRON, artificial ventilation must be continued until spontaneous breathing is restored. Repeated dosages 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 ED_{90} (135 mg per kg body weight) was administered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, peripherally acting agents

ATC Code: M03AC09

Mechanism of Action

MYOCRON (rocuronium bromide) is a fast onset, intermediate acting non-depolarising neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate.

This action is antagonised 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 rocuronium bromide. The ED95 in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg/kg respectively).

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with 0.6 mg/kg rocuronium bromide is 30–40 minutes. The total duration (time until spontaneous recovery to 90% of control twitch height) is 50 minutes. The mean time of spontaneous recovery of twitch response from 25 to 75% after a bolus dose of 0.6 mg/kg rocuronium bromide is 14 minutes ($1\text{-}1^{1/2}$ x $ED_{90)}$ With lower dosages of 0.3-0.45 mg/kg rocuronium bromide, onset of action is slower and duration of action is shorter. With 2 mg / kg high doses, the clinical duration is 110 minutes.

Intubation during routine anesthesia

Within 60 seconds following intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (2 x 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 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 rocuronium bromide. Of these, 70% are rated excellent. The duration of clinical effect with this dose approaches 1 hour, and at the end of the time the neuromuscular block can be safely reversed. Following a dose of 0.6 mg/kg rocuronium bromide, adequate intubation conditions are achieved within 60 seconds in 81% and 75% of the patients during a rapid sequence induction technique with propofol or fentanyl/thiopental, respectively.

Special populations:

Pediatric patients:

Mean onset time in infants and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. Time to relax and wake up is shorter in children than in babies and adults (1 min) (0.4, 0.6 and 0.8 minutes).

The resting phase and the duration of convalescence tend to be shorter in children than in infants and adults. When the pediatric age groups were compared, the mean time to T3 recurrence was found in in newborns and infants 56.7 and 60.7 min, respectively, when compared to new walking children, it was in children and adolescents 45.4, 37.6 and 42.9 minutes, respectively.

During sevoflurane / nitric oxide and isoflurane / nitric oxide (maintanence) anesthesia (pediatric patients) (PP group) following 0.6 mg/kg rocuronium initial intubation dose* mean (SD) starting time and clinical duration)

	Maximum blockage duration ** (min)	Recurrence time of T3** (min)
Newborns (0-27 days) n=10	0.98 (0.62)	56.69 (37.03) n=9
Infants (28 days-2 months)	0.44 (0.19) n=10	60.71 (16.52)
Babies (3 months-23 months)	0.59 (0.27)	45.46 (12.94) n=27
Children (aged 2-11)	0.84 (0.29)	27.58 (11.82)
Adolescents (aged 12-17)	0.98 (0.38)	42.90 (15.83) n=30

* Rocuronium Dose applied within 5 seconds

** Rocuronium intubation dose calculated at the end of the application.

Elderly patients and patients with hepatic and / or cerebrovascular disease and / or renal disease

The duration of action of maintenance doses of 0.15 mg/kg rocuronium bromide might be somewhat longer under enflurane and isoflurane anesthesia in geriatric patients and in patients with hepatic and/or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous 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

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

Cardiovascular surgery

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

Reversal of muscle relaxation

Administration of acetylcholinesterase inhibitors, (neostigmine, pyridostigmine or edrophonium) at reappearance of T2 or at the first signs of clinical recovery, antagonizes the action of rocuronium bromide.

5.2 Pharmacokinetics Properties

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

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.
Metabolites were not detected in plasma.

Pediatric patients

Pharmacokinetics of Rocuronium bromide ranging in children aged from 0 to 17 years (n = 146) was evaluated in dataset of two clinical trials under pharmacokinetics, sevoflurane (induction) and isoflurane / nitrosoxide maintainance) anesthesia in pediatric patients. All pharmacokinetic parameters showed linearity similar to body weight (1 hr^{-1}.\ kg^{-1}). Distribution volume and elimination half life (h) decreases with age (year). Typical pediatric pharmacokinetic parameters in each age group are summarized below:

Rocuronium bromide estimated PK parameters (mean [SD]), sevoflurane and nitrous oxide (induction) and isoflurane (nitrate oxide (maintanance anesthesia) in typical pediatric patients)

PK parameters	Patient age range				
	Newborns (0-27 days)	Infants (28 days-2 months)	Babies (3-23 months)	Children (2-11 years old)	Adolescents (12-17 years)
CL (L/kg/hr)	0.3 (0.07)	0.30 (0.08)	0.33 (0.10)	0.35 (0.09)	0.29 (0.14)
Distribution volume (L/kg)	0.42 (0.06)	0.31 (0.03)	0.23 (0.03)	0.18 (0.02)	0.18 (0.01)
T½βhr)	1.1 (0.02)	0.9 (0.3)	0.8 (0.2)	0.7 (0.2)	0.8 (0.3)

Elderly patients and patients with hepatic and / or biliary system disorders or renal system disorders

In controlled studies the plasma clearance in geriatric patients and in patients with renal dysfunction was reduced, in most studies however without reaching the level of statistical significance. In patients with hepatic disease, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 ml/kg/min (see section 4.2)

In infants (3 months to 1 year), the apparent volume of distribution at steady state conditions is increased compared to adults and children (1-8 years). In older children (3-8 years), a trend is seen towards higher clearance and shorter elimination half-life (approximately 20 minutes) compared to adults, younger children and infants.

Intensive care unit

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 differences between patient variability was 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 (± SS) elimination half-life of 21.5 (± 3.3) hours, a volume of distribution at steady state of 1.5 (± 0.8) l/kg and a plasma clearance of 2.1 (± 0.8) ml/kg/min were found.

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.

No animal studies with rocuronium bromide have been performed to assess carcinogenic potential. Mutagenic studies with rocuronium bromide (Ames test, chromosomal aberration assay and micronucleus test in mammalian cells) were carried out and no mutagenic potential was observed.

There is no proper animal model to mimic the usually extremely complex clinical situation of the ICU patient. Therefore the safety of MYOCRON when used to facilitate mechanical ventilation in the Intensive Care Unit is mainly based on results obtained in clinical studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium acetate

Sodium chloride

Acetic acid

Water for injection

6.2.Incompatibilities

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

Rocuronium bromide must not be mixed with other medicinal products except those mentioned as compatible (see section 6.6)

If rocuronium bromide must be administered via the same infusion line that is also used for other drugs which have been identified as incompatible or have not been proven to be compatible, it is important that this infusion line is adequately flushed (e.g. with 0.9% NaCl).

6.3. Shelf life

Shelf life of MYOCRON is 36 months on condition that storing under the prescribed conditions (see section .6.4). Date that specified on box and label of vial is expiration date; this is the last date MYOCRON can be used. Solution should be used up immediately after opening because MYOCRON does not contain any preservative substance.

After dilution with infusion fluids (see section 6.6); stability in chemical and physical use was shown to be for 72 hours at 30 ° C.

Diluted product should be used immediately point of view microbiological. If, it does not use immediately, user/director is responsible to storage time and conditions and cannot be more than 24 hours between 2 - 8 ° C if dilution is not achieved with controlled and approved aseptic conditions.

6.4. Special precautions for storage

MYOCRON should be stored at 2°-8°C in refrigerator. It can be stored outside of the refrigerator at a temperature of up to 25°C for a maximum 6 months. The product should not be placed back into the refrigerator, once it has been kept outside. The storage period must not exceed the shelf-life.

6.5. Nature and contents of container

1 and 10 5 ml Type I colorless glass vial / box containing 50 mg rocuronium bromide.

6.6. Special precautions for disposal and other handling

Compatibleness studies were performed with infusion solution that were specified the following below. Rocuronium bromide was compatible at 0.5mg/ml and 2.0mg/ml nominal concentrations with 0.9% NaCl, 5% dextrose, 5% dextrose in saline (salt water), sterile water for infusion, Ringer Lactate and Haemaccel.

Administration should be started immediately after mixing and it should be completed within 24 hours. Unused solutions should be disposed.

7. MARKETING AUTHORIZATION HOLDER

VEM İlaç San. ve Tic. A.Ş.

Söğütözü Mahallesi 2177. Cadde No:10 B/49

Çankaya/ANKARA/TURKEY

Tel: + 90 312 427 43 57-58

Fax: + 90 312 427 43 59

8. MARKETING AUTHORIZATION NUMBER(S)

244/58

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization in TR: 31.08.2012

License renewal date:

10. DATE OF REVISION OF THE TEXT