SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MUSCOBLOC 50 mg/5 mL Solution for I.V. Injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each ml of MUSCOBLOC contains 10 mg rocuronium bromide.

Excipients:

1 vial contains:

Sodium acetate..... 10 mg

Sodium Chloride.....16.5 mg

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

MUSCOBLOC is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine sequence induction and to provide skeletal muscle relaxation during surgery. MUSCOBLOC is required as additional therapy for intubation and mechanical ventilation in the intensive care unit (ICU).

4.2. Posology and method of administration

Like other neuromuscular blocking agents, MUSCOBLOC 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 MUSCOBLOC should be individualized in each patient. The method of anaesthesia 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.

Anaesthetics administered by inhalation do potentiate the neuromuscular blocking effects of MUSCOBLOC. This potentiation however, becomes clinically relevant in the course of anaesthesia, when the volatile agents have reached the tissue concentrations required for this interaction.

Consequently, adjustments with MUSCOBLOC should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of MUSCOBLOC during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (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 anaesthesia 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 anaesthesia. After that dose 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 anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

For use of rocuronium bromide during rapid sequence induction of anaesthesia in patients undergoing Caesarean section reference is made to section 4.6.

Higher doses

When there was a reason for the selection of higher doses in individual patients, rocuronium bromide up to 2 mg / kg was administered as an initial dose during surgery without adverse cardiovascular effects. The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of action (see section 5.1).

Maintenance dosing

The recommended maintenance dose is 0.15 mg/kg rocuronium bromide; in the case of long-term inhalational anaesthesia 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 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 rocuronium bromide and, when neuromuscular block starts to weaken, 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 anaesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6 mg/kg/h and under general anaesthesia 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 anaesthetic method used.

Additional information on special populations

Pediatric population

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 anaesthesia 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 the same initial infusion rates as for adults are recommended and then this infusion rate 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 recommendations for the use of rocuronium bromide in newborns (0-1 months).

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 (elderly) 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 anaesthesia is 0.6 mg/kg rocuronium bromide. A dose of 0.6 mg/kg should be considered for rapid sequence induction of anaesthesia in patients in which a prolonged duration of action is expected. Regardless of the anaesthetic 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 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 dose:

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 stimulation. Dosage should always be titrated to individual effect in patients. 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. This dose 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 inter-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/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.

Administration:

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

Special populations:

Renal and Hepatic Failure:

Because rocuronium is excreted in urine and bile, it should be used with caution in patients with clinically significant hepatic and renal diseases and/or failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg/kg rocuronium bromide.

Pediatric population

It is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric patients due to a lack of data on safety and efficacy.

Geriatric population:

It is not recommended for the facilitation of mechanical ventilation in the intensive care in geriatric patients due to a lack of data on safety and efficacy.

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

Since MUSCOBLOC 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 should be expected that intubation difficulties may arise, especially when used as part of the rapid sequence induction technique.

As with other neuromuscular blocking agents, residual neuromuscular blockade has been reported for MUSCOBLOC. Geriatric patients (65 years or older) 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 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.

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 the heart rate.

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 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.

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

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

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 rocuronium bromide.

Prolonged circulation time

Conditions associated with prolonged circulation time such as cardiovascular disease, old age and 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 a reduced plasma clearance.

Neuromuscular disease

Like other neuromuscular blocking agents, MUSCOBLOC 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 severity and nature of this change can vary greatly. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of MUSCOBLOC may have profound effects and MUSCOBLOC should be titrated to the response.

Hypothermia

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

Obesity

Like other neuromuscular blocking agents, MUSCOBLOC 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 MUSCOBLOC

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

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

This medicinal product contains less than 1 mmol (23 mg) sodium per ml, i.e it is essentially "sodium free".

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 MUSCOBLOC

Increased effect:

- Halogenated volatile anaesthetics potentiate the neuromuscular block of MUSCOBLOC. The effect only becomes apparent with maintenance dose (see section 4.2). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
- After intubation with succinylcholine (see section 4.4).
- Long-term concomitant use of corticosteroids and MUSCOBLOC in the ICU may result in prolonged duration of neuromuscular block or myopathy (see section 4.4 and 4.8).
- Other medicines:
- Antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.
- diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lidocaine intravenous bupivacaine epidural) and acute administration of phenytoin or ß-blocking agents.

Recurarisation 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.
- Calcium chloride, potassium chloride.
- Protease inhibitors (gabexate, ulinastatin).

Variable effect:

- Administration of other non-depolarizing neuromuscular blocking agents in combination with MUSCOBLOC may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.
- Succinylcholine given after the administration of MUSCOBLOC may produce potentiation or attenuation of the neuromuscular blocking effect of MUSCOBLOC.

Effect of MUSCOBLOC on other drugs:

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

4.6. Pregnancy and lactation

General recommendation:

Pregnancy category is C.

Women with childbearing potential / Contraception

During treatment with rocuronium, women with childbearing potential should be advised to use effective contraceptive methods.

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 MUSCOBLOC to pregnant women.

Caesarean section

In patients undergoing Caesarean section, it can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic agent is administered or following suxamethonium facilitated intubation. However, MUSCOBLOC, administered in doses of 0.6 mg/kg may not produce adequate conditions for intubation until 90 seconds after administration. This dose has been shown to be safe in pregnant women undergoing Caesarean section. MUSCOBLOC does not affect APGAR score, fetal muscle tone or cardio-respiratory 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 anaesthesia, 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 MUSCOBLOC should be reduced and be titrated to twitch response.

Lactation

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

Reproduction ability / Fertility

No studies were conducted with animals to assess the carcinogenic potential of rocuronium bromide or its damage to fertility.

4.7. Effects on ability to drive and use machines

Since MUSCOBLOC is used as an adjunct to general anaesthesia, the usual precautionary measures after a general anaesthesia 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.

The adverse reactions are listed below according to system organ class: 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);

Not known (Cannot be estimated from the available data)

MedDRA SOC	Preferred Term[1]	
	Uncommon (≥ 1/1,000 to ≤ 1/100) / Rare (≥ 1/10.000 to ≤ 1/1.000)[2]	Very rare (≤1/10 000)
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 Flushing
Respiratory, thoracic and mediastinal disorders		Bronchospasm
Skin and subcutaneous tissue disorders		Angioneurotic oedema[1] 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 oedema[1] Malign hyperthermia
Injury and poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anaesthesia

[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 two rather than five categories.

[3] after long-term use in the intensive care unit

Anaphylaxis

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

Anaphylaxis/ anaphylactoid reactions: bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse – shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume they may occur and take the necessary precautions.

Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematous 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.

<u>Prolonged neuromuscular block</u>

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

Myopathy

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

Local injection site reactions

Pain was reported at the injection site during the rapid sequential anesthesia induction, especially if the patient has not lost his consciousness more fully and especially when propofol is used as an induction agent.In clinical studies, injection-related pain was observed in 16% of patients undergoing rapid sequential anesthesia induction with propofol and in 0.5% of patients undergoing rapid sequential anesthesia induction with fentanyl and thiopental.

Pediatric patients:

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

4.9. Overdose and therapy

In the event of overdose and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. 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 in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of MUSCOBLOC, 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 ED_{90} (135 mg/kg rocuronium bromide) was administered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: Muscle relaxants, peripherally acting agents

ATC Code: M03AC09

Mechanism of Action:

MUSCOBLOC (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 ED_{90} (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during intravenous anaesthesia is approximately 0.3 mg/kg rocuronium bromide. The ED_{95} 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% (recovery index) after a bolus dose of 0.6 mg/kg rocuronium bromide is 14 minutes. With lower dosages of 0.3-0.45 mg/kg rocuronium bromide (1 -1½ x ED_{90}), onset of action is slower and duration of action is shorter. With high doses of 2 mg/kg, clinical duration is 110 minutes.

Intubation during routine anaesthesia

Within 60 seconds following intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (2 x ED_{90} under intravenous anaesthesia), 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 anaesthesia under propofol or fentanyl/thiopental anaesthesia, 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 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 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, toddlers and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. Comparison within 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). Comparing within pediatric age groups demonstrated that mean time to reappearance of T3 was prolonged in neonates and infants (56.7 and 60.7 min., respectively) when compared to toddlers, children and adolescents (45.4, 37.6 and 42.9 min., respectively).

Mean (SD) time to onset and clinical duration following 0.6 mg/kg rocuronium initial intubating dose* during sevoflurane/nitrous oxide and isoflurane/nitrous oxide (maintenance) anaesthesia (pediatric patients) PP group

	Time to maximum block ** (min)	Time to reappearance of T3 **(min)
Neonates (0-27 days) n=10	0,98 (0,62)	56,69 (37,03) n=9

Inflants (28 days-2 months)	0,44 (0,19) n=10	60,71 (61,52)
Toddlers (3 months - 23 months)	0,59 (0,27)	45,46 (12,94) n=27
Children (2-11 years)	0,84 (0,29)	37,58 (11,82)
Adolescents (12-17 years)	0,98 (0,38)	42,90 (15,83) n=30

* Dose of rocuronium administered within 5 seconds.

** Calculated from the end of administration of the rocuronium 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 rocuronium bromide might be somewhat longer under enflurane and isoflurane anaesthesia 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 anaesthesia (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 TOF (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 T2 to TOF stimulation and recovery of TOF ratio to 0.7 approximates 1.5 hours, ranging from 1 to 5 hours in patients without multiple organ failure and 4 hours, ranging from 1 to 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, antagonises the action of MUSCOBLOC.

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.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours. Following injection of a radiolabeled dose of rocuronium bromide, excretion of the radiolabel is on average 47% in urine and 43% in faeces after 9 days. Approximately 50% is recovered as the parent compound. No metabolites are detected in plasma.

Pediatric patients:

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 under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anesthesia. 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 pediatrics within each age group are summarized below:

Estimated PK parameters (Mean [SD]) of rocuronium bromide in typical paediatric patients during sevoflurane and nitrous oxide (induction) and isoflurane/nitrous oxide (maintenance anaesthesia)

PK Parameters	Patient age range				
	Neonates (0-27 days)	Inflants (28 days-2 months)	Toddlers (3 - 23 months)	Children (2-11 age)	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)
Distribution volume (L/kg)	0,42 (0,06)	0,31 (0,03)	0,23 (0,03)	0,18 (0,02)	0,18 (0,01)
$T_{1/2}\beta$(hr)	1,1 (0,02)	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 disease and/or renal failure:
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-1 year), the volume of distribution in steady-state conditions increases compared to adults and children (1-8 years). In older children (3-8 years); there is a higher tendency towards higher clearance and shorter elimination half-life (about 20 minutes) than 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 volume of distribution at steady state are increased. A

large inter-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 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.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours. Following injection of a radiolabeled dose of rocuronium bromide, excretion of the radiolabel is on average 47% in urine and 43% in faeces 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.

Animal studies with rocuronium bromide were not performed to evaluate the carcinogenic potential. Mutagenic studies with rocuronium bromide (Ames test, chromosomal aberration analysis in myeloma cells and micronucleus test) were conducted and no mutogenic potential was revealed.

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

. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

MUSCOBLOC contains the following excipients: sodium acetate, sodium chloride, acetic acid (as pH adjuster), water for injection. No preservative has been added

6.2. Incompatibilities

Physical incompatibility has been documented for MUSCOBLOC 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. MUSCOBLOC is incompatible with intralipid.

It is not recommended to mix MUSCOBLOC in the same bag or syringe with other solutions or medicines other than those indicated to be compatible (see section "Instructions for use").

If MUSCOBLOC is administered via the same infusion line that is also used for other drugs for which incompatibility has been demonstrated or for which compatibility has not been established., it is important that this infusion line is adequately flushed (e.g. with 0.9% NaCl).

6.3. Shelf-life

MUSCOBLOC has a shelf life of 24 months, 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 MUSCOBLOC may be used. Since MUSCOBLOC 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

Storage in the Refrigerator

Store at 2°-8°C in the refrigerator.

Storage out of the refrigerator

It may be stored outside of the refrigerator at a temperature of up to 30°C for a maximum 12 weeks. 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

MUSCOBLOC 50 mg/5 ml

Packaging of 5 vials each containing 50 mg rocuronium bromide.

Packaging of 10 vials each containing 50 mg rocuronium bromide.

6.6. Special precautions for disposal and other handling

Compatibility studies with the following infusion fluids have been performed. In nominal concentrations of 0.5 mg/ml and 2.0 mg/ml MUSCOBLOC 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. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

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