Summary of Product Characteristics for Pharmaceutical Products

1.Name of Medicinal Product

Rocutroy 10 mg/ml Solution for Injection

2.Qualitative and quantitative composition

1 ml solution contains 10 mg Rocuronium Bromide.

For the full list of excipients, see section 6.1

3.Pharmaceutical Form

Solution for Injection

A clear, colorless to slightly yellow colored solution.

4. Clinical Particulars:

4.1 Therapeutic indications

Rocuronium bromide is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, to provide skeletal muscle relaxation, during surgery. It is also indicated 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, Rocutroy 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 Rocutroy should be individualised 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.

Inhalational anaesthetics do potentiate the neuromuscular blocking effects of Rocutroy. 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 Rocutroy should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Rocutroy during long lasting procedures (longer than 1 hour) under inhalational anaesthesia.

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 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 anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

Higher doses

Should there be reason for selection of larger doses in individual patients, there is no indication from clinical studies that the use of initial doses up to 2 mg/kg rocuronium bromide is associated with an increased frequency or severity of cardiovascular effects. The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of action.

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 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 anaesthesia, 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 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.

Paediatric 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.

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

Thus, for children (2-11 years) the same initial infusion rates as for adults are recommended and then 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.

The experience with rocuronium bromide in rapid sequence induction in paediatric patients is limited. Rocuronium bromide is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in paediatric 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 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).

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 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/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 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/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.

Special populations

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

Method of administration

Rocutroy is administered intravenously either as a bolus injection or as a continuous infusion

4.3 Contraindications

Rocuronium bromide is contra-indicated in patients with hypersensitivity to rocuronium bromide or to the bromide ion or to any of the excipients.

4.4 Special warnings and precautions for use

Since Rocutroy 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.

As with other neuromuscular blocking agents, residual neuromuscular blockade has been reported for Rocutroy. In order to prevent complications resulting from residual neuromuscular blockade, 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 neuromuscular blockade 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 (such as sugammadex or acetylcholinesterase inhibitors) should be considered, especially in those cases where residual neuromuscular blockade is more likely to occur.

High rates of cross-sensitivity between neuromuscular blocking agents have been reported. Therefore, where possible, before administering Rocutroy, hypersensitivity to other neuromuscular blocking agents should be excluded. Rocutroy should only be used when absolutely essential in susceptible patients. Patients who experience a hypersensitivity reaction under general anaesthesia should be tested subsequently for hypersensitivity to other neuromuscular blockers.

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 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-depolarising 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 Rocutroy 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 Rocutroy:

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 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, Rocutroy 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 myasthenic (Eaton-Lambert) syndrome, small doses of Rocutroy may have profound effects and Rocutroy should be titrated to the response.

Hypothermia

In surgery under hypothermic conditions, the neuromuscular blocking

effect of Rocutroy is increased and the duration prolonged.

Obesity

Like other neuromuscular blocking agents, Rocutroy 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-depolarising neuromuscular blocking agents. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of Rocutroy.

Hypokalaemia (e.g. after severe vomiting, diarrhoea and diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, 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-depolarising neuromuscular blocking agents.

Effect of other drugs on Rocutroy

Increased effect:

• Halogenated volatile anaesthetics potentiate the neuromuscular block of Rocutroy. The effect only becomes apparent with maintenance dosing. Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.

• After intubation with suxamethonium.

• Long-term concomitant use of corticosteroids and Rocutroy in the ICU may result in prolonged duration of neuromuscular block or myopathy.

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 anaesthetics (lidocaine i.v, 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.

Decreased effect:

• Prior chronic administration of phenytoin or carbamazepine.

• Calcium chloride, potassium chloride.

• Protease inhibitors (gabexate, ulinastatin).

Variable effect:

• Administration of other non-depolarising neuromuscular blocking agents in combination with Rocutroy 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 Rocutroy may produce potentiation or attenuation of the neuromuscular blocking effect of Rocutroy.

Effect of Rocutroy on other drugs

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

Paediatric population

No formal interaction studies have been performed. The above mentioned interactions for adults and their special warnings and precautions for use should be taken into account for paediatric patients.

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 Rocutroy to pregnant women.

Caesarean section

In patients undergoing Caesarean section, Rocutroy 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, Rocutroy, 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 parturients undergoing Caesarean section. Rocutroy does not affect Apgar score, foetal 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.

Breast-feeding

It is unknown whether rocuronium bromide is excreted in human breast milk. Animal studies have shown insignificant levels of rocuronium bromide in breast milk.

Insignificant levels of rocuronium bromide were found in the milk of lactating rats. There are no human data on the use of Rocutroy during lactation. Rocutroy 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 Rocutroy 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 frequency of undesirable effects is classified into the following categories:

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

The most common undesirable effects are pain/reaction around injection site, changes in vital functions and prolonged neuromuscular block.

The adverse events are as follows:

Immune system disorders

Very rare: Anaphylactic reaction e.g. anaphylactic shock, Anaphylactoid shock, Anaphylactoid reaction and Hypersensitivity

Nervous system disorders

Very rare : Flaccid Paralysis

Cardiac disorders

Uncommon/rare: Tachycardia

Vascular disorders

Uncommon/rare: Hypotension

Very rare : Circulatory collapse and shock, flushing

Respiratory, thoracic, and mediastinal disorders

Very rare : Bronchospasm

Skin and subcutaneous tissue disorders

Very rare: Rash, erythematous rash, Angioneurotic oedema, Urticaria

Musculoskeletal disorders and connective tissue disorders

Very rare: Skeletal muscle weakness and Steroid myopathy

General disorders and administration site conditions

Uncommon/rare: Injection site pain/reaction, drug ineffective, drug effect/therapeutic response decreased

Very rare: Face oedema, malignant hyperthermia

Injury, poisoning and procedural complications

Uncommon/rare: Prolonged neuromuscular block, Delayed recovery from anaesthesia

Very rare: Airway complication of anaesthesia

Anaphylaxis

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Rocutroy, have been reported. Anaphylactic/anaphylactoid reactions are: 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 generalised histaminoid (anaphylactoid) reactions (see also under anaphylactic reactions above) should always be taken into consideration when administering these drugs.

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

Local injection site reactions

During rapid sequence induction of anaesthesia, 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 anaesthesia with propofol and in less than 0.5% of the patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

Paediatric population

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%.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

In the event of overdosage 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 Rocutroy, 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 rocuronium bromide) was administered.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of Action

Rocutroy (rocuronium bromide) is a fast onset, intermediate acting nondepolarising 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 endplate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

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 (6680) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193214) ml/kg and plasma clearance is 3.7 (3.53.9) ml/kg/min.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 1224 hours. After 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.

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 Rocuronium bromide 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 chloride

Water for injections

Sodium acetate (Tri Hydrate)

Glacial acetic acid

6.2 Incompatibilities:

Physical incompatibility has been documented for Rocutroy 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.

If Rocutroy 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 Rocutroy and drugs for which incompatibility with Rocutroy has been demonstrated or for which

compatibility with Rocutroy has not been established.

6.3 Shelf-life:

Unopened Vials: 24 months

After dilution with infusion fluids, chemical and physical in-use stability has been demonstated 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 between 2°C to 8°C, protected from light

Rocutroy may also be stored outside of the refrigerator at a temperature of up to 30°C for a maximum 12 weeks, after which it should be discarded. 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

5 ml flint tubular vial USP Type- I with 20 mm bromo butyl rubber closure and 20 mm light pink flip off seal. Such 1 vial packed in printed carton along with Insert

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 Rocutroy 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 medicinal product or waste material should be disposed of in accordance with local requirements

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder

Name: Roikaa Pharmaceuticals Ltd

Address: Commerce House- 1, Satya Marg, Off Judges Bungalow Road, Bodakdev, Ahmedabad-380054.

Country: India.

Manufacturing site addresses

Name:	Troikaa Pharmaceuticals Ltd
Address:	C-1 Sara Industrial Estate, Selaqui, Dehradun-248 197, Uttarakhand
Country:	India.

8. Marketing authorization number

H2024/CTD6538/12830

9. Date of first registration

16/02/2024

10. Date of revision of the text

November 2024