Public Assessment Report

Decentralised Procedure

Rocuronium Bromide 10mg/ml Solution for Injection or Infusion

UK/H/1312/001/DC
UK licence no: PL00289/1083

TEVA UK Limited
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted TEVA UK Limited a Marketing Authorisation (licence) for the medicinal product Rocuronium Bromide 10mg/ml Solution for Injection or Infusion (PL 00289/1083). This is a prescription-only medicine (POM).

Rocuronium bromide belongs to a group of medicines called muscle relaxants. Normally the nerves send messages to the muscles by impulses. Rocuronium bromide acts by blocking these impulses so that the muscles become relaxed. This medicine is given to relax the muscles in the body during surgery to make it easier for the surgeon to operate. Rocuronium bromide may also be used to ease the insertion of a tube into the trachea (windpipe) for artificial ventilation (mechanical assistance of breathing).

The test product was considered the same as the reference product Esmeron 10 mg/l solution for injection held by NV Organon authorised since 6 April 1994.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Rocuronium Bromide 10mg/ml Solution for Injection or Infusion outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

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<th><strong>Product Name</strong></th>
<th>Rocuronium Bromide 10 mg/ml solution for injection</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<td><strong>Active Substance</strong></td>
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<td><strong>Form</strong></td>
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<td><strong>MA Holder</strong></td>
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Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Rocuronium Bromide 10mg/ml Solution for Injection or Infusion is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Rocuronium Bromide 10 mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection or infusion contains 10 mg rocuronium bromide.
Each vial with 2.5 ml contains 25 mg rocuronium bromide.
Each vial with 5 ml contains 50 mg rocuronium bromide.
Each vial with 10 ml contains 100 mg rocuronium bromide.
Excipient(s): 3.6 mg sodium per ml.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion
Clear, colourless to yellow-orange solution
pH of the solution: 3.6 to 4.4
Osmolality: 250-310 mOsmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rocuronium bromide solution for injection or infusion is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation, during surgery. It is also indicated as an adjunct in the intensive care unit (ICU) (e.g. to facilitate intubation), for short term use. See also section 4.2 and 5.1.

4.2 Posology and method of administration

As with other neuromuscular blocking agents, the dosage of rocuronium bromide solution for injection or infusion 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 medicinal products 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 the neuromuscular block and recovery.

Inhalational anaesthetics potentiate the neuromuscular blocking effects of rocuronium bromide solution for injection or infusion. This potentiation becomes clinically relevant during the course of anaesthesia when a certain tissue concentration of the volatile agents is reached. Consequently, adjustments should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of rocuronium bromide solution for injection or infusion 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 guidance for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the intensive care unit.

This medicinal product is for single use only.

Surgical Procedures

Tracheal intubation:
The standard intubating dose during routine anaesthesia is 0.6 mg/kg rocuronium bromide, which results in adequate intubation conditions 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 also 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.

Maintenance dosage:
The recommended maintenance dose is 0.15 mg/kg rocuronium bromide. In case of long-term inhalational anaesthesia it 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 (TOF) are present.

**Continuous infusion:**
If rocuronium bromide solution for injection or infusion is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg/kg rocuronium bromide and, when the 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 the neuromuscular block at this level ranges from 0.3-0.6 mg/kg/h. Under inhalational anaesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h.

Continuous monitoring of the neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

**Dosage in pregnant patients:**
In patients undergoing Caesarean section, it is recommended to only use a dose of 0.6 mg/kg rocuronium bromide, since a 1.0 mg/kg dose has not been investigated in this patient group. Reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxaemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of rocuronium should be reduced and be titrated to twitch response.

**Dosage in paediatric patients:**
For infants (28 days-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. For continuous infusion in paediatrics, the infusion rates, with exception of children, are the same as for adults. For children higher infusion rates might be necessary. For children the same initial infusion rates as for adults are recommended and this should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to train-of-four stimulation during the procedure. The experience with rocuronium bromide in rapid sequence induction in paediatric patients is limited. Rocuronium bromide is therefore not recommended for facilitation tracheal intubation conditions during rapid sequence induction in paediatric patients.

There are no data to support recommendations for the use of rocuronium bromide in new-born infants (0-1 month).

**Dosage 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 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, however adequate conditions for intubation may not be established for 90 seconds after administration of rocuronium bromide. 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 also Continuous infusion).

**Dosage in 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.

**Administration**
Rocuronium bromide solution for injection or infusion is administered intravenously (i.v.) either as a bolus injection or as a continuous infusion (see section 6.6). Administration should be begun immediately after mixing, and should be completed within 24 hours.

**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**
Rocuronium bromide solution for injection or infusion should be administered only by experienced staff familiar with the use of neuromuscular blocking agents. Adequate facilities and staff for endotracheal intubation and artificial ventilation have to be available for immediate use.
Since Rocuronium bromide solution for injection or infusion 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 is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique.

As with other neuromuscular blocking agents, residual curarisation has been reported for Rocuronium. In order to prevent complications resulting from residual curarisation, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Other factors which could cause residual curarisation 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 curarisation is more likely to occur.

It is essential to ensure that the patient is breathing spontaneously, deeply and regularly before leaving the theatre after anaesthesia.

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.

Dose levels higher than 0.9 mg/kg rocuronium bromide may increase the heart rate; this effect could counteract the bradycardia produced by other anaesthetic agents or by vagal stimulation.

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 done by or under supervision of experienced clinicians who are familiar with the effects and with appropriate neuromuscular monitoring techniques.

Because Rocuronium bromide is always used with other agents and because of the possibility of the occurrence of malignant hyperthermia during anaesthesia, even in the absence of known triggering agents, clinicians should be familiar with the early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anaesthesia. In animal studies it was shown that rocuronium bromide is not a triggering factor for malignant hyperthermia.

Myopathy has been reported after long-term concurrent use of non-depolarising neuromuscular blockers and corticosteroids. The co-administration period should be reduced to be as short as possible (see section 4.5).

Rocuronium bromide should only be administered after full recovery from the neuromuscular blockade caused by suxamethonium.

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

- **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 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 diseases, old age and an oedematous state resulting in an increased volume of distribution, may contribute to a slower onset of action.

- **Neuromuscular disease**
  Like other neuromuscular blocking agents, rocuronium bromide 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 rocuronium bromide may have profound effects and rocuronium bromide solution for injection or infusion should be titrated to the response.

- **Hypothermia**
  In surgery under hypothermic conditions, the neuromuscular blocking effect of rocuronium bromide injection is increased and the duration prolonged.
• **Obesity**
  Like other neuromuscular blocking agents, rocuronium bromide 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 Rocuronium bromide**

- Hypokalaemia (e.g. after severe vomiting, diarrhoea or diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnia and cachexia.
- Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

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

The following medicinal products have been shown to influence the magnitude and/or duration of the effect of non-depolarising neuromuscular blocking agents:

**Effect of other medicinal products on Rocuronium bromide solution for injection or infusion**

#### Increased effect:
- Halogenated volatile anaesthetics
- High doses of: thiopental, methohexital, ketamine, fentanyl, gammahydroxybutyrate, etomidate and propofol
- Other non-depolarising neuromuscular blocking agents.
- Prior administration of suxamethonium (see section 4.4)
- Long term concomitant use of corticosteroids and rocuronium in the ICU may result in prolonged duration of neuromuscular block or myopathy (see sections 4.4 and 4.8).

Other medicinal products:
- Antibiotics: aminoglycosides, lincosamides (e.g. lincomycin and clindamycin), polypeptide antibiotics, acylamino-penicillin antibiotics, tetracyclines, high doses of metronidazole.
- Diuretics, thiamine, MAO inhibiting agents, quinidine and its isomer quinine, protamine, adrenergic blocking agents, magnesium salts, calcium channel blocking agents, lithium salts and local anaesthetics (lidocaine i.v., bupivacaine epidural).

#### Decreased effect:
- Neostigmine, edrophonium, pyridostigmine, aminopyridine derivatives
- Prior chronic administration of corticosteroids, phenytoin or carbamazepine
- Noradrenaline, azathioprine (only transient and limited effect), theophylline, calcium chloride, potassium chloride
- Protease inhibitors.

#### Variable effect:
- Administration of other non-depolarising neuromuscular blocking agents in combination with rocuronium bromide 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 rocuronium bromide may produce potentiation or attenuation of the neuromuscular blocking effect of rocuronium bromide.

**Effect of rocuronium bromide solution for injection or infusion on other medicinal products**

Combined use with lidocaine could result in a more instant effect of lidocaine. 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).
4.6 Pregnancy and lactation

Pregnancy

There are very limited data on the use of rocuronium bromide during human pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Rocuronium bromide solution for injection or infusion should only be given to pregnant women when strictly necessary and the attending physician decides that the benefits outweigh the risks. Use of rocuronium bromide during caesarean section at doses of 0.6 mg/kg does not effect the Apgar score, the foetal muscle tone or the 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 reactions in the new-born infant.

Note: doses of 1.0 mg/kg have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients.

Lactation

It is unknown whether rocuronium bromide is excreted in human breast milk. Animal studies have shown excretion of rocuronium bromide in insignificant amounts in breast milk. Other medicinal products of this class show little excretion into breast milk and low resorption by the suckling child.

A decision on whether to continue/discontinue breast-feeding should be made taking into account the benefit of breast-feeding and the potential risk to the child.

4.7 Effects on ability to drive and use machines

Rocuronium bromide has a major influence on the ability to drive and use machines. It is not recommended to use potentially dangerous machinery or to drive a car during the first 24 hours after the full recovery from the neuromuscular blocking action of rocuronium bromide.

4.8 Undesirable effects

The frequency of undesirable effects is classified into the following categories:

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥1/10</td>
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<tr>
<td>Common</td>
<td>≥1/100 to &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥1/1,000 to &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10,000 to &lt;1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Not known</td>
<td>cannot be estimated from the available data</td>
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</tbody>
</table>

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

Adverse reactions are listed below, by system organ class and absolute frequency (all reported events).

**Immune system disorders**

Very rare:
- Anaphylactic reaction e.g. anaphylactic shock
- Anaphylactoid reaction*
- Hypersensitivity

**Nervous system disorders**

Very rare:
- Paralysis

**Cardiac disorders**

Very rare:
- Tachycardia

**Vascular disorders**

Very rare:
- Hypotension
- Circulatory collapse and shock
Respiratory, thoracic, and mediastinal disorders  
Very rare:  
• Bronchospasm  
Not known:  
• Apnoea  
• Respiratory failure

Skin and subcutaneous tissue disorders  
Very rare:  
• Rash, erythematous rash  
• Angioedema  
• Urticaria  
• Itching  
• Exanthema

Musculoskeletal and connective tissue disorders  
Not known:  
• Skeletal muscle weakness  
• Steroid myopathy (see section 4.4)

General disorders and administration site conditions  
Very common:  
• Injection site pain/reaction*

Investigations  
Very rare:  
• Increased histamine level*

Injury, poisoning and procedural complications  
Very rare:  
• Prolonged neuromuscular block*

*Additional information on adverse reactions:  
Increased histamine level  
Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally and systemically, the possible occurrence of itching and erythematous reaction at the site of injection and/or generalised histaminoid (anaphylactoid) reactions such as bronchospasm and cardiovascular changes e.g. hypotension and tachycardia should always be taken into consideration when administering these drugs. Rash, exanthema, urticaria, bronchospasm and hypotension have been reported very rarely in patients given rocuronium bromide. In clinical studies only a slight increase in mean plasma histamine level 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 non-depolarising blocking agents as a class consists of an extension of the agent’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 apnoea.

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.

Anaphylactic reaction
Severe anaphylactic reactions to neuromuscular blocking agents have been reported to be fatal in some cases. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions.

4.9 Overdose
In the event of overdose and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. Upon start of spontaneous recovery an acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of rocuronium bromide, 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 ED90 (135 mg/kg rocuronium bromide) was administered.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: muscle relaxants, peripherally acting agents, other quaternary ammonium compounds.
ATC code: M03AC09
Pharmacodynamics
Rocuronium bromide is an intermediate acting non-depolarising neuromuscular blocking agent with a fast onset, possessing all of the characteristic pharmacological actions of this class of medicinal products (curariform). It acts by competing for nicotinic cholinoreceptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.
The ED90 (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during balanced anaesthesia is approximately 0.3 mg/kg rocuronium bromide.
Routine practice
Within 60 seconds after intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (2 x ED90 under balanced anaesthesia), adequate intubation conditions can be achieved in nearly all patients. In 80% of these patients intubation conditions are rated excellent. Within 2 minutes general muscle paralysis adequate for any type of procedure is established. The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with this dose 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 2 x ED90), the onset of the effect is slower and duration of action is shorter (13-26 minutes). After administration of 0.45 mg/kg rocuronium bromide, acceptable intubation conditions are reached after 90 seconds.
Emergency intubation
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, after administration of 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. After administration of 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.
Doses higher than 1.0 mg/kg rocuronium bromide will not improve the intubation conditions appreciably; the duration of the effect, however, will be prolonged. Doses higher than 4 x ED90 have not been studied.
Intensive Care
The use of rocuronium in the Intensive Care Unit was studied in two open-label trials. A total of 95 adult patients were treated with an initial dose of 0.6 mg/kg rocuronium bromide, followed by a continuous infusion of 0.2-0.5 mg/kg/h during the first hour of administration as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train-of-four (TOF) stimulation. The dosages were individually titrated. In the following hours, doses were decreased under regular monitoring of the TOF stimulation. Administration for a time period of up to 7 days has been investigated.
- Adequate neuromuscular blockade was achieved, but a high variability in hourly infusion rates between patients and a prolonged recovery from neuromuscular blockade was observed.
- The time to recover of the train-of-four ratio to 0.7 is not significantly correlated to the total duration of rocuronium 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 varied between 0.8 and 12.5 hours in patients without multiple organ failure and 1.2 – 25.5 hours in patients with multiple organ failure.

- Special populations
  The mean time to effect after 0.6mg/kg is shorter in infants and children compared to adults. The duration of effect is shorter in children compared to adults.
  The duration of the effect of maintenance doses of 0.15 mg rocuronium bromide per kg body weight might be somewhat longer under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous anaesthesia (approximately 13 minutes). No cumulation of effect (progressive increase in duration of action) with repetitive maintenance doses at the recommended level has been observed.

Cardiovascular surgery
In patients scheduled for cardiovascular surgery the most common cardiovascular changes during the onset of maximum blockage after receiving a dose of 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.

Antagonists
Administration of acetylcholinesterase inhibitors, such as neostigmine, pyridostigmine or edrophonium, antagonises the action of rocuronium bromide.

5.2 Pharmacokinetic properties
After intravenous administration of a single bolus dose of rocuronium bromide solution for injection or infusion, the time course of the plasma concentration 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 the plasma clearance is 3.7 (3.5-3.9) ml/kg/min.

The plasma clearance in geriatric patients and in patients with renal dysfunction is slightly reduced compared to younger patients with normal renal function. In patients with hepatic diseases, 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).

The apparent volume of distribution in infants (3-12 months) is higher compared to older children (1-8 years) and adults. In children aged 3-8 years, clearance is higher and the elimination half-life is approximately 20 minutes shorter compared to adults and children < 3 years.

When administered as a continuous infusion to facilitate mechanical ventilation for a time period of 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A high variability between patients was found in controlled clinical studies, related to the nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean (±SD) elimination half-life of 21.5 (±3.3) hours, an (apparent) 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 bromide 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 faeces after 9 days. Approximately 50% is recovered as rocuronium bromide. No metabolites are detected in the plasma.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and genotoxicity. Carcinogenicity studies have not been performed with rocuronium bromide.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium acetate trihydrate
Acetic acid, glacial
Sodium chloride
Sodium hydroxide 10% solution (for pH adjustment)
Water for injections
6.2 Incompatibilities
Physical incompatibility has been documented for rocuronium bromide when added to solutions containing the following active substance: 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.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
Unopened vial: 1 year
Opened vial: The product should be used immediately after opening the vial.
After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°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
Before opening: Store in a refrigerator (2–8°C)
Storage out of the refrigerator:
Rocuronium bromide solution for injection or infusion may also be stored below 25°C for up to 3 months, after which it should be discarded. Once stored at 8-25°C Rocuronium bromide should not be returned to the refrigerator. The date at which the product is taken out of the refrigerator should be written on the specific site on the outer carton. The total storage time (including storage of unopened vial outside of the refrigerator) must not exceed 12 months.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container
Colourless glass vials (type I) closed with chlorobutyl rubber stopper and aluminium flip off cap.
Content of the vials: 2.5 ml, 5 ml or 10 ml.
2.5 ml vials: Pack sizes of 1 or 10 vials
5 ml vials: Pack sizes of 1, 10, 12 or 60 vials
10 ml vials: Pack sizes of 1, 10 or 20 vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused solutions should be discarded.
The solution is to be visually inspected prior to use. Only clear solutions free from particles should be used.
Rocuronium bromide solution for injection or infusion has been shown to be compatible with: sodium chloride 9 mg/ml (0.9%), glucose 50 mg/ml (5%), glucose 50 mg/ml (5%) in sodium chloride 9 mg/ml (0.9%), water for injections, Lactated Ringers solution and Polygeline solution for infusion (3.5%).
If rocuronium bromide solution for injection or infusion is administered via the same infusion line with other medicinal products, it is important that the infusion line is adequately flushed (e.g. with sodium chloride 9 mg/ml (0.9 %) solution for infusion) between administration of rocuronium bromide solution for injection or infusion and medicinal products for which incompatibility with rocuronium bromide has been demonstrated or for which compatibility with rocuronium bromide has not been established.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited,
Brampton Road,
Hampden Park,
Eastbourne,
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1083
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/03/2010

10 DATE OF REVISION OF THE TEXT
23/03/2010
Module 3
Product Information Leaflet

Package leaflet information for the user
Rocuronium bromide 10 mg/ml Solution for Injection or Infusion

What Rocuronium Bromide 10 mg/ml Solution for Injection or Infusion is and What it is used for
Rocuronium bromide belongs to a group of medicines called muscle relaxants. Normally, the nerves send messages to the muscles by impulses. Rocuronium bromide acts by blocking these impulses so that the muscles become relaxed. When you have an operation your muscles must be completely relaxed. This makes it easier for the surgeon to perform the operation. Rocuronium bromide may also be used if you are having an anaesthesia, so to protect the patient usually your doctors (anaesthetists) will carry out procedures to allow mechanical ventilation (mechanical assistance of breathing).

Before Rocuronium Bromide 10 mg/ml Solution for Injection or Infusion is used
Do NOT use Rocuronium Bromide:
- If you are allergic (hypersensitive) to rocuronium bromide or the bromide ion or any of the other ingredients of Rocuronium bromide.
- If you have any of the following conditions which may influence the effects of Rocuronium bromide for example:
  - Low calcium level in the blood (hypocalcaemia)
  - Low potassium level in the blood (hypokalaemia)
  - High magnesium level in the blood (hypermagnesaemia)
  - Low levels of protein in the blood (hypoproteinaemia)
  - Too much carbon dioxide in the blood (hypercarbia)
  - Too much acid in the blood or body tissues (acidoosis)

To be told special with Rocuronium Bromide:
Before you receive the medicine you must tell your doctor or anaesthetist if you have or have had any of the following conditions:
- Kidney, heart or liver disease
- Diabetes affecting nerves and muscles (polyneuropathy, myasthenia gravis, Eaton-Lambert syndrome)
- Allergy to any other muscle relaxants
- A slow heart beat (bradycardia)
- A serious condition called malignant hyperthermia where you have a very high fever

When you are told:
If you suffer from certain conditions which may influence the effects of Rocuronium bromide for example:
- Low calcium level in the blood (hypocalcaemia) which can occur after blood transfusion
- Low potassium level in the blood (hypokalaemia)
- High magnesium level in the blood (hypermagnesaemia)
- Low levels of protein in the blood (hypoproteinaemia)
- Too much carbon dioxide in the blood (hypercarbia)
- Too much acid in the blood or body tissues (acidosis)

Preparation guide for use with Rocuronium Bromide 10 mg/ml Solution for Injection or Infusion
(For full details regarding this product please refer to the SPC.)
The following information is intended for medical or healthcare professionals only.
Rocuronium bromide solution for injection or infusion should be administered only by experienced staff familiar with the use of muscle relaxants including the use of resuscitation equipment. Adequate facilities and staff for resuscitation and artificial ventilation have to be available for immediate use.

Incompatibilities
Physical incompatibility has been documented for rocuronium bromide when added to solutions containing the following active substance:
- Amphotericin B
- Acyclovir
- Cefotaxime
- Ceftriaxone
- Ciprofloxacin
- Cefuroxime
- Dexamethasone sodium succinate
- Doxycycline
- Encomycin
- Gentamicin
- Isoniazid
- Methicillin
- Metronidazole
- Ampicillin
- Captopril
- Cyclosporcin
- Erythromycin
- Pantrocin
- Phenytoin
- Penicillin G
- Pilocarpine
- Procainamide
- Propofol
- Quinidine
- Streptomycin
- Theophylline
- Trimethoprim

This medicinal product must not be mixed with other medicinal products except those mentioned in the following section.

Storage of product:
Rocuronium bromide solution for injection or infusion has been shown to be compatible with sodium chloride 9mg/ml (0.9%).
DCPAR Rocuronium bromide 10mg/ml Solution for Injection or Infusion

Your anesthetist will take into account the anesthetic, the expected duration of surgery, your body weight, other medicines you have been given and your state of health.

Rocuronium bromide will be given to you by your anesthetist. It is given intravenously, either as a single injection or as a continuous infusion.

If you are given more Rocuronium bromide than you should, your anesthetist will monitor your condition during the procedure. It is unlikely that you will be given too much Rocuronium bromide. However, if this happens and your lungs are not working, your anesthetist will make sure that you continue breathing artificially until you can breathe on your own. You may need to be kept asleep while recovery takes place because this is not reversed.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

Possible Side Effects

Like all medicines, Rocuronium bromide can cause side effects, although not everyone gets them.

If the following happens tell your doctor immediately:

- An asthmatic reaction causing swelling of the lips, face or neck, leading to severe difficulty in breathing, skin rash or hives.

This is a very rare but serious side effect. You may need urgent medical attention.

The following side effects have been reported at the approximate frequencies shown:

<table>
<thead>
<tr>
<th>Very common</th>
<th>affects more than 1 in 10</th>
<th>Rare</th>
<th>affects 1 in 10,000 or less</th>
<th>Very rare</th>
<th>affects less than 1 in 10,000</th>
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</tbody>
</table>

Very common:
- Palpitations
- Headache
- Dry mouth
- Nasal congestion
- Abnormal renal function
- Dizziness
- Chills
- Nausea
- Vomiting
- Diarrhoea
- Constipation
- Confusion
- Irritability
- Restlessness
- Complaints of taste
- Midgut irritation
- Other discomfort in the abdomen
- Abdominal bloating
- Feeling hot
- Blisters
- Sweating
- Shaking
- Leg cramps
- Infections (including urinary tract, skin and respiratory infections)
- Numbness and tingling
- Nerve damage
- Oedema
- Allergic reactions
- Serious allergic reactions causing difficulty in breathing or dizziness
- Allergic shock
- Complete loss of strength in a limb or muscle (paralysis)
- Increase in heart rate (tachycardia)
- Drop in blood pressure (hypotension)
- An emergency when the organs and tissues are not receiving enough blood (circulatory collapse and shock)
- Intraocular pressure (in the eye)
- Severe allergic reaction which causes swelling of the face or throat
- Rash, nettle rash, itching
- Increase in histamine levels which can lead to itching, rash, wheezing and changes in heart rate
- Long period of muscle relaxation leading to muscle weakness or loss of strength (paralysis)
- Uncommon:
- Loss of taste
- Severe breathing problems (respiratory failure)
- Inflammation
- Muscle disease associated with the use of steroids
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Store information

See section 7 "How to store rocuronium bromide Teva.”

Special precautions for handling

For intravenous use only as a bolus injection or as a continuous infusion. Administration should be given immediately after mixing and should be completed within 24 hours.

This medicinal product is for single use only, any unused solutions should be discarded.

The solution is to be visually inspected prior to use. Only clear solutions free from particles should be used.

Disposal

Any unused product or waste material should be disposed of in accordance with local recommendations.

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Module 4
Labelling
Rocuronium Bromide 10mg/ml Solution for Injection or Infusion

Label
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Rocuronium Bromide 10mg/ml Solution for Injection or Infusion, to be used as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, to provide skeletal muscle relaxation, during surgery and as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation, is approvable.

This is an application is submitted under Article 10(1) of Directive 2001/83 (as amended) for Rocuronium Bromide 10mg/ml Solution for Injection or Infusion. It has been shown to be a generic medicinal product of the originator product Esmeron 10 mg/ml solution for injection held by NV Organon authorised since 6 April 1994; hence the 10 year rule is fulfilled.

Rocuronium is a non-depolarizing neuromuscular blocking agent and belongs to the curariform class of drugs. The drug is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. It is also indicated as an adjunct in the intensive care unit to facilitate intubation and mechanical ventilation.

The application is in accordance with Article 10(1) of Directive 2001/83/EC as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, pre-clinical and clinical overviews have been submitted.

No new non-clinical or clinical efficacy studies were conducted, which is acceptable given that the application was for a generic version of a product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorises as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, “close-out letters” or “exchange of information” issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are inplace at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has
necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an ERA is justified since the application is for a generic version of an approved product and it is not likely to change the total market of rocuronium bromide.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Rocuronium bromide 10 mg/ml solution for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Rocuronium bromide</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>M03AC09 Peripherally acting muscle relaxant</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>10mg/ml solution for injection or infusion</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1312/001/DC</td>
</tr>
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<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Belgium, Denmark, France, Germany, Hungary, Italy, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Slovenia, Slovakia and Spain</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 00289/1083</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, BN22 9AG</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Rocuronium bromide

General Information

Nomenclature

Name: Rocuronium bromide

Chemical name: 1-[17β-(Acetyloxy)-3 α-hydroxy-2 β-(morpholin-4-yl)-5 α-androstan-16β-yl]-1-(prop-2-enyl) pyrrolidinium bromide

Structure

Description: An almost white or pale yellow, slightly hygroscopic powder

Molecular formula: C_{32}H_{53}BrN_{2}O_{4}

Relative molecular mass: 610

Solubility: freely soluble in water and in anhydrous ethanol

The active substance, rocuronium bromide, is the subject of a European Pharmacopeia (Ph.Eur.) monograph.

Manufacture

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance rocuronium bromide.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active substance.

An appropriate specification is provided for the active substance rocuronium bromide, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided for 5 batches and comply with the proposed specification. Suitable Certificates of Analysis have been provided for all reference standards used by the active substance manufacturer during validation studies.
The active substance is stored in amber glass (Ph. Eur. Type III) flask, which is first placed in a double layered polyethylene bag and then into an aluminium bag. Desiccant pads and oxygen scavengers are placed between the primary and secondary container. Relevant specifications and satisfactory Certificates of Analysis are provided for the packaging components. Appropriate declarations have been provided stating that the primary packaging components comply with the food contact requirements of Directive 2002/72/EC, (as amended).

Satisfactory specifications and certificates have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated for the drug substance and supports an appropriate retest period when stored in the proposed packaging.

**DRUG PRODUCT**

**Other ingredients**

The drug product is presented as a clear colourless to yellow-orange solution for injection or infusion. Rocuronium Bromide 10mg/ml Solution for Injection or Infusion is available in three proportionally formulated strengths: 25mg/2.5ml, 50mg/5ml and 100mg/10ml. All strengths contain 10mg of rocuronium bromide per ml.

Other ingredients consist of pharmaceutical excipients, sodium acetate trihydrate, glacial acetic acid, sodium chloride, sodium hydroxide 10% solution (pH adjustment) and water for injections. An appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph.Eur monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

There were no novel excipients used and no overages.

**Pharmaceutical Development**

The aim is to develop a pharmaceutical form similar to the innovator product, Esmeron Solution for injection (NV Oraganon). The composition of the proposed product has the same qualitative composition (except for sodium hydroxide), dosage form, strength, route of administration as the reference product.

All excipients are commonly used in parenteral products and their function has been satisfactorily explained.

Both test and reference products are administered as an aqueous intravenous solution containing the same active substance in the same concentration, therefore no bioequivalence study is required.

A satisfactory summary of the manufacturing process development is provided.

**Compatibility**

Compatibility studies have demonstrated that the product is compatible with the proposed packaging. Container integrity is demonstrated and is satisfactory.
**Impurity Profiles**
Comparative impurity profile studies between the proposed product and the reference product show that the same identified impurities are found in both test and reference products.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture.

Process validation data was performed on eight pilot scale batches. Validation data was provided for the main steps of the manufacturing process. All results are consistent and well within the acceptable limits.

**Finished product specification**
The finished product specification is satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory process validation data are provided for three consecutive production scale batches for the 10 ml and 5 ml fill size. Validation data for three consecutive batches of 2.5 ml fill size at production scale will be provided prior to launch of the product which is satisfactory. Suitable Certificates of Analysis have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**
The finished product is filled into colourless Type I glass vials closed with chlorobutyl rubber stoppers and aluminium flip off caps. The vials contain 2.5ml, 5ml or 10ml solution for injection or infusion containing 25mg, 50mg or 100mg of rocuronium bromide respectively, to give a solution of 10mg/ml.

The 2.5ml vials are either packaged individually or in a pack size of 10 vials.
The 5ml vials are packaged individually or in pack sizes of 10,12 or 60 vials.
The 10ml vials are packaged individually or in pack sizes of 10 or 20 vials

The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory.

**Stability**
Stability studies were performed a total of eight pilot batches for all presentations of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 1 year for an unopened product with storage conditions “Store in a refrigerator (2-8°C)”

For storage conditions and advice for use and handling of the solution once opened, refer to the SmPC. Acceptable in-use stability studies were conducted and the results provided to support the statements made in the SmPC. The SmPC also contains information on disposal of the product.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labelling are pharmaceutically acceptable.

MAA form
The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic product of the proposed and originator products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and reference products.

II NON-CLINICAL ASSESSMENT

II.1. Critical evaluation of the Non-Clinical Overview
Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacokinetic and toxicological properties of rocuronium bromide, which is widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For a generic application of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal product, Esmeron 10 mg/l solution for injection. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by a suitably qualified person. The overview cites 22 references, the majority from the published literature, dated 1993 to 2006 and is satisfactory.

II.2 Conclusions
There are no objections to approval of Rocuronium Bromide 10mg/ml solution for injection or infusion.

III.3 CLINICAL ASPECTS

INTRODUCTION
This application is a generic application referring to the reference medicinal product Esmeron, 10 mg/ml solution for injection which has been authorised for more than 10 years in at least a Member state or in the Community. According to Article 10(1) of Directive 2001/83/EC, for this type of application, the applicant is not required to provide results of clinical trials.

The product proposed for marketing authorisation is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference product Esmeron. Thus, in accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence”, (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.
Assessor's comment: No new data have been submitted and none are required.

Biowaiver

The product proposed for marketing authorisation is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference product Esmeron. Thus, in accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

Post marketing experience

No post-marketing data is available. The medicinal product has not been marketed in any country.

The applicant has not requested a different PSUR cycle upon approval. The RMS considers the submission of 6-monthly PSURs not necessary and recommends PSUR submissions to be aligned with the EU Harmonised Birthday and related Data Lock Points as published on the HMA website.

Benefit-Risk assessment

The application contains an adequate review of published clinical data. Approval is recommended from the clinical point of view.

Summary of Product Characteristics

This is satisfactory.

Patient Information Leaflet and Labels

These are satisfactory.

CONCLUSIONS

The efficacy and safety of the product are satisfactory for the grant of a product licence.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Rocuronium Bromide 10mg/ml Solution for Injection or Infusions is well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with that for the reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with rocuronium bromide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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