Public Assessment Report

Decentralised Procedure

DC PAR

Cisatracurium 2 mg/ml Solution for Injection/Infusion
Cisatracurium 5 mg/ml Solution for Injection/Infusion

UK/H/3758/001-2/DC

UK licence no: PL 04515/0234-5

Hospira UK Limited
Lay Summary

On 20 October 2011, the Medicine and Healthcare products Regulatory Agency (MHRA) granted Hospira UK Limited Marketing Authorisations (licences) for the medicinal products Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion (PL 04515/0234-5). These licences were granted via the decentralised procedure (UK/H/3758/001-2/DC). These are prescription-only medicines.

Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion contain the active ingredient cisatracurium besilate and belongs to a group of medicines called muscle relaxants. Cisatracurium is used:

- during surgery and other procedures and in intensive care
- with general anaesthesia, or sedation in the Intensive Care Unit to relax muscles
- to help insert a tube into the windpipe (tracheal intubation) if a person needs help to breathe (with or without a machine)

Cisatracurium is used in adults and in children over 1 month of age.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion outweigh the risks and Marketing Authorisations were granted.
# TABLE OF CONTENTS

Module 1: Information about initial procedure  
Module 2: Summary of Product Characteristics  
Module 3: Patient Information Leaflets  
Module 4: Labelling  
Module 5: Scientific Discussion  
  I Introduction  
  II About the product  
  III.1 Quality aspects  
  III.2 Non-clinical aspects  
  III.3 Clinical aspects  
  IV Overall Conclusion and Benefit:Risk Assessment  
Module 6: Steps taken after initial procedure
## Module 1

| **Product Name** | Cisatracurium 2 mg/ml Solution for Injection  
| | Cisatracurium 5 mg/ml Solution for Injection |
| **Type of Application** | Generic Application, Article 10(1) |
| **Active Substance** | Cisatracurium besilate |
| **Form** | Solution for Injection |
| **Strength** | 2 mg/ml  
| | 5 mg/ml |
| **Marketing Authorisation Holder** | Hospira UK Limited  
| | Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, UK |
| **Reference Member State (RMS)** | UK |
| **Concerned Member State (CMS)** | Austria, Belgium, Cyprus, Czech Republic, Denmark, Germany, Estonia, France, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Slovakia and Spain. |
| **Procedure Number** | UK/H/3758/001-2/DC |
| **End of Procedure** | 22 August 2011 |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summaries of Product Characteristics (SmPC) for Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion (PL 04515/0234-5) are as follows: Differences between strengths are highlighted in yellow.

1 NAME OF THE MEDICINAL PRODUCT
Cisatracurium 2 mg/mL Solution for Injection/Infusion
Cisatracurium 5 mg/mL Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Cisatracurium 2 mg as cisatracurium besilate 2.7 mg per 1 ml
Cisatracurium 5 mg as cisatracurium besilate 6.7 mg per 1 ml

For PL 04515/0234
One vial of 2.5 ml contains 5 mg of cisatracurium as cisatracurium besilate 6.7 mg
One vial of 5 ml contains 10 mg of cisatracurium as cisatracurium besilate 13.4 mg
One vial of 10 ml contains 20 mg of cisatracurium as cisatracurium besilate 26.8 mg

PL 04515/0235
One vial of 30 ml contains 150 mg of cisatracurium as cisatracurium besilate 200.7 mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Solution for injection/infusion

Colourless to pale yellow or greenish yellow solution

pH: 3.0 – 3.7

For PL 04515/0234
Osmolarity: 8 mOsmol/l

For PL 04515/0235
Osmolarity: 17 mOsmol/l

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Cisatracurium is indicated for use during surgical and other procedures and in intensive care in adults and children aged 1 month and over. It can be used as an adjunct to general anaesthesia, or sedation in the Intensive Care Unit (ICU) to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation.

4.2 Posology and method of administration
Cisatracurium should only be administered by or under the supervision of anaesthetists or other clinicians who are familiar with the use and action of neuromuscular blocking agents. Facilities for tracheal intubation and maintenance of pulmonary ventilation and adequate arterial oxygenation have to be available

Cisatracurium should not be mixed in the same syringe or administered simultaneously through the same needle as propofol injectable emulsion or with alkaline solutions such as sodium thiopentone (see section 6.2).

This medicinal product contains no antimicrobial preservative and is intended for single patient use.

Monitoring advice
As with other neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of cisatracurium in order to individualise dosage requirements.

**Use by intravenous bolus injection**

**Dosage in adults**

**Tracheal Intubation:** The recommended intubation dose of cisatracurium for adults is 0.15 mg/kg (body weight). This dose produced good to excellent conditions for tracheal intubation 120 seconds after administration of cisatracurium, following induction of anaesthesia with propofol.

Higher doses will shorten the time to onset of neuromuscular block.

The following table summarises mean pharmacodynamic data when cisatracurium was administered at doses of 0.1 to 0.4 mg/kg (body weight) to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

<table>
<thead>
<tr>
<th>Initial Cisatracurium Dose mg/kg (body weight)</th>
<th>Anaesthetic Background</th>
<th>Time to 90% T1* Suppression (min)</th>
<th>Time to Maximum T1* Suppression (min)</th>
<th>Time to 25% Spontaneous T1* Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>Opioid</td>
<td>3.4</td>
<td>4.8</td>
<td>45</td>
</tr>
<tr>
<td>0.15</td>
<td>Propofol</td>
<td>2.6</td>
<td>3.5</td>
<td>55</td>
</tr>
<tr>
<td>0.2</td>
<td>Opioid</td>
<td>2.4</td>
<td>2.9</td>
<td>65</td>
</tr>
<tr>
<td>0.4</td>
<td>Opioid</td>
<td>1.5</td>
<td>1.9</td>
<td>91</td>
</tr>
</tbody>
</table>

*T1* Single twitch response as well as the first component of the train-of-four response of the adductor pollicis muscle following supramaximal electrical stimulation of the ulnar nerve.

Enflurane or isoflurane anaesthesia may extend the clinically effective duration of an initial dose of cisatracurium by as much as 15%.

**Maintenance:** Neuromuscular block can be extended with maintenance doses of cisatracurium. A dose of 0.03 mg/kg (body weight) provides approximately 20 minutes of additional clinically effective neuromuscular block during opioid or propofol anaesthesia.

Consecutive maintenance doses do not result in progressive prolongation of effect.

**Spontaneous Recovery:** Once spontaneous recovery from neuromuscular block is underway, the rate is independent of the cisatracurium dose administered. During opioid or propofol anaesthesia, the median times from 25 to 75% and from 5 to 95% recovery are approximately 13 and 30 minutes, respectively.

**Reversal:** Neuromuscular block following cisatracurium administration is readily reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T2: T1 ratio ≥ 0.7) are approximately 4 and 9 minutes respectively, following administration of the reversal agent at an average of 10% T1 recovery.

**Dosage in paediatric patients**

**Tracheal Intubation (paediatric patients aged 1 month to 12 years):** As in adults, the recommended intubation dose of cisatracurium is 0.15 mg/kg (body weight) administered rapidly over 5 to 10 seconds. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection of cisatracurium. Pharmacodynamic data for this dose are presented in the tables below.

Cisatracurium has not been studied for intubation in ASA Class III-IV paediatric patients. There are limited data on the use of cisatracurium in paediatric patients under 2 years of age undergoing prolonged or major surgery.
In paediatric patients aged 1 month to 12 years, cisatracurium has a shorter clinically effective duration and a faster spontaneous recovery profile than those observed in adults under similar anaesthetic conditions. Small differences in the pharmacodynamic profile were observed between the age ranges 1 to 11 months and 1 to 12 years which are summarised in the tables below.

**Paediatric Patients aged 1 to 11 months**

<table>
<thead>
<tr>
<th>Cisatracurium Dose mg/kg (body weight)</th>
<th>Anaesthetic Background</th>
<th>Time to 90% Suppression (min)</th>
<th>Time to Maximum Suppression (min)</th>
<th>Time to 25% Spontaneous T1 Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 Halothane</td>
<td></td>
<td>1.4</td>
<td>2.0</td>
<td>52</td>
</tr>
<tr>
<td>0.15 Opioid</td>
<td></td>
<td>1.4</td>
<td>1.9</td>
<td>47</td>
</tr>
</tbody>
</table>

**Paediatric Patients aged 1 to 12 years**

<table>
<thead>
<tr>
<th>Cisatracurium Dose mg/kg (body weight)</th>
<th>Anaesthetic Background</th>
<th>Time to 90% Suppression (min)</th>
<th>Time to Maximum Suppression (min)</th>
<th>Time to 25% Spontaneous T1 Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 Halothane</td>
<td></td>
<td>2.3</td>
<td>3.0</td>
<td>43</td>
</tr>
<tr>
<td>0.15 Opioid</td>
<td></td>
<td>2.6</td>
<td>3.6</td>
<td>38</td>
</tr>
</tbody>
</table>

When cisatracurium is not required for intubation: A dose of less than 0.15 mg/kg can be used. Pharmacodynamic data for doses of 0.08 and 0.1 mg/kg for paediatric patients aged 2 to 12 years are presented in the table below:

<table>
<thead>
<tr>
<th>Cisatracurium Dose mg/kg (body weight)</th>
<th>Anaesthetic Background</th>
<th>Time to 90% Suppression (min)</th>
<th>Time to Maximum Suppression (min)</th>
<th>Time to 25% Spontaneous T1 Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.08 Halothane</td>
<td></td>
<td>1.7</td>
<td>2.5</td>
<td>31</td>
</tr>
<tr>
<td>0.1 Opioid</td>
<td></td>
<td>1.7</td>
<td>2.8</td>
<td>28</td>
</tr>
</tbody>
</table>

Administration of cisatracurium following suxamethonium has not been studied in paediatric patients (see section 4.5).

Halothane may be expected to extend the clinically effective duration of a dose of cisatracurium by up to 20%. No information is available on the use of cisatracurium in children during anaesthesia with other halogenated fluorocarbon anaesthetic agents, but these agents may also be expected to extend the clinically effective duration of a dose of cisatracurium.

**Maintenance (paediatric patients aged 2-12 years):** Neuromuscular block can be extended with maintenance doses of cisatracurium. In paediatric patients aged 2 to 12 years, a dose of 0.02 mg/kg (body weight) provides approximately 9 minutes of additional clinically effective neuromuscular block during halothane anaesthesia. Consecutive maintenance doses do not result in progressive prolongation of effect.

There are insufficient data to make a specific recommendation for maintenance dosing in paediatric patients under 2 years of age. However, very limited data from clinical studies in paediatric patients under 2 years of age suggest that a maintenance dose of 0.03mg/kg may extend clinically effective neuromuscular block for a period of up to 25 minutes during opioid anaesthesia.
Spontaneous Recovery: Once recovery from neuromuscular block is underway, the rate is independent of the cisatracurium dose administered. During opioid or halothane anaesthesia, the median times from 25 to 75% and from 5 to 95% recovery are approximately 11 and 28 minutes, respectively.

Reversal: Neuromuscular block following cisatracurium administration is readily reversible with standard doses of anti-cholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery ($T_2:T_1$ ratio $>0.7$) are approximately 2 and 5 minutes respectively, following administration of the reversal agent at an average of 13% $T_1$ recovery.

Use by intravenous infusion

Dosage in adults and children aged 2 to 12 years
Maintenance of neuromuscular block may be achieved by infusion of cisatracurium. An initial infusion rate of $3 \mu g/kg$ (body weight)/min ($0.18 \mu g/kg/hr$) is recommended to restore 89 to 99% $T_1$ suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 to 2 $\mu g/kg$ (body weight)/min ($0.06$ to $0.12 \mu g/kg/hr$) should be adequate to maintain block in this range in most patients.

Reduction of the infusion rate by up to 40% may be required when cisatracurium is administered during isoflurane or enflurane anaesthesia (see section 4.5).

The infusion rate will depend upon the concentration of cisatracurium in the infusion solution, the desired degree of neuromuscular block, and the patient's weight. The following table provides guidelines for delivery of undiluted cisatracurium.

**Infusion Delivery Rate of Cisatracurium injection 2 mg/ml**

<table>
<thead>
<tr>
<th>Patient (body weight) (kg)</th>
<th>Dose (µg/kg/min)</th>
<th>Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>20</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>70</td>
<td>2.1</td>
<td>3.2</td>
</tr>
<tr>
<td>100</td>
<td>3.0</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Steady rate continuous infusion of cisatracurium is not associated with a progressive increase or decrease in neuromuscular blocking effect.

Following discontinuation of infusion of cisatracurium, spontaneous recovery from neuromuscular block proceeds at a rate comparable to that following administration of a single bolus.

Dosage in neonates (aged less than 1 month)

The use of cisatracurium in neonates is not recommended as it has not been studied in this patient population.

Dosage in elderly patients
No dosing alterations are required in elderly patients. In these patients cisatracurium has a similar pharmacodynamic profile to that observed in young adult patients but, as with other neuromuscular blocking agents, it may have a slightly slower onset.

Dosage in patients with renal impairment
No dosing alterations are required in patients with renal failure.
In these patients cisatracurium has a similar pharmacodynamic profile to that observed in patients with normal renal function but it may have a slightly slower onset.

Dosage in patients with hepatic impairment
No dosing alterations are required in patients with end-stage liver disease. In these patients cisatracurium has a similar pharmacodynamic profile to that observed in patients with normal hepatic function but it may have a slightly faster onset.

**Dosage in patients with cardiovascular disease**

When administered by rapid bolus injection (over 5 to 10 seconds) to adult patients with serious cardiovascular disease (New York Heart Association Class I-III) undergoing coronary artery bypass graft (CABG) surgery, cisatracurium has not been associated with clinically significant cardiovascular effects at any dose studied (up to and including 0.4 mg/kg (8x ED₉₅)). However, there are limited data for doses above 0.3 mg/kg in this patient population.

Cisatracurium has not been studied in children undergoing cardiac surgery.

**Dosage in Intensive Care Unit (ICU) patients**

Cisatracurium may be administered by bolus dose and/or infusion to adult patients in the ICU.

An initial infusion rate of cisatracurium of 3 µg/kg (body weight)/min (0.18 mg/kg/hr) is recommended for adult ICU patients. There may be wide interpatient variation in dosage requirements and these may increase or decrease with time. In clinical studies the average infusion rate was 3 µg/kg/min [range 0.5 to 10.2 µg/kg (body weight)/min (0.03 to 0.6 mg/kg/hr)]

The median time to full spontaneous recovery following long-term (up to 6 days) infusion of cisatracurium in ICU patients was approximately 50 minutes.

**Infusion Delivery Rate of Cisatracurium injection 5 mg/ml**

<table>
<thead>
<tr>
<th>Patient (body weight) (kg)</th>
<th>Dose (µg/kg/min)</th>
<th>Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>1.2</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>2.4</td>
<td>3.6</td>
</tr>
</tbody>
</table>

The recovery profile after infusions of cisatracurium to ICU patients is independent of duration of infusion.

4.3 **Contraindications**

This medicinal product is contra-indicated in patients known to be hypersensitive to cisatracurium, atracurium, or benzenesulfonic acid.

4.4 **Special warnings and precautions for use**

Cisatracurium paralyses the respiratory muscles as well as other skeletal muscles but has no known effect on consciousness or pain threshold. Cisatracurium should be only administered by or under the supervision of anaesthetists or other clinicians who are familiar with the use and action of neuromuscular blocking agents. Facilities for tracheal intubation and maintenance of pulmonary ventilation and adequate arterial oxygenation have to be available.

Caution should be exercised when administering this medicinal product to patients who have shown hypersensitivity to other neuromuscular blocking agents since a high rate of cross-sensitivity (greater than 50%) between neuromuscular blocking agents has been reported (see section 4.3).

Cisatracurium does not have significant vagolytic or ganglion-blocking properties. Consequently, there is no clinically significant effect on heart rate and will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery.

Patients with myasthenia gravis and other forms of neuromuscular disease have shown greatly increased sensitivity to non-depolarising blocking agents. An initial dose of not more than 0.02 mg/kg is recommended in these patients.
Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking agents.

There is no information on the use of this medicinal product in neonates aged less than one month since it has not been studied in this patient population.

Cisatracurium has not been studied in patients with a history of malignant hyperthermia. Studies in malignant hyperthermia-susceptible pigs indicated that cisatracurium does not trigger this syndrome.

There have been no studies of cisatracurium in patients undergoing surgery with induced hypothermia (25 to 28°C). As with other neuromuscular blocking agents the rate of infusion required to maintain adequate surgical relaxation under these conditions may be expected to be significantly reduced.

Cisatracurium has not been studied in patients with burns; however, as with other non-depolarising neuromuscular blocking agents, the possibility of increased dosing requirements and shortened duration of action must be considered if cisatracurium injection is administered to these patients.

Cisatracurium is hypotonic and must not be applied into the infusion line of a blood transfusion.

**Intensive Care Unit (ICU) Patients:**

When administered to laboratory animals in high doses, laudanosine, a metabolite of cisatracurium and atracurium, has been associated with transient hypotension and in some species, cerebral excitatory effects. In the most sensitive animal species, these effects occurred at laudanosine plasma concentrations similar to those that have been observed in some ICU patients following prolonged infusion of atracurium.

Consistent with the decreased infusion rate requirements of cisatracurium, plasma laudanosine concentrations are approximately one third those following atracurium infusion.

There have been rare reports of seizures in ICU patients who have received atracurium and other agents. These patients usually had one or more medical conditions predisposing to seizures (e.g. cranial trauma, hypoxic encephalopathy, cerebral oedema, viral encephalitis, uraemia). A causal relationship to laudanosine has not been established.

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

Many drugs have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents, including the following:-

**Increased Effect:**

By anaesthetic agents such as enflurane, isoflurane, halothane (see section 4.2) and ketamine, by other non-depolarising neuromuscular blocking agents or by other drugs such as antibiotics (including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin), anti-arrhythmic drugs (including propranolol, calcium channel blockers, lignocaine, procainamide and quinidine), diuretics, (including frusemide and possibly thiazides, mannitol and acetazolamide), magnesium and lithium salts and ganglion blocking drugs (trimetaphan, hexamethonium).

A decreased effect is seen after prior chronic administration of phenytoin or carbamazepine.

Prior administration of suxamethonium has no effect on the duration of neuromuscular block following bolus doses of cisatracurium or on infusion rate requirements.

Administration of suxamethonium to prolong the effects of non-depolarising neuromuscular blocking agents may result in a prolonged and complex block which can be difficult to reverse with anticholinesterases.

Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to non-depolarising neuromuscular blocking agents might result. Such drugs include various antibiotics, b-blockers (propranolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), anti-rheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.
Treatment with anticholinesterases, commonly used in the treatment of Alzheimer's disease e.g. donepezil, may shorten the duration and diminish the magnitude of neuromuscular blockade with cisatracurium.

4.6 Fertility, pregnancy and lactation
There is insufficient data on the use of cisatracurium in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/fetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown.

Cisatracurium should not be used during pregnancy.

It is not known whether cisatracurium or its metabolites are excreted in human milk. A risk to the breast-feeding child cannot be excluded. Due to the short half-life, an influence on the breast-feeding child is not to be expected if the mother restarts breast-feeding after the effects of the substance have worn off. As a precaution breast-feeding should be discontinued during treatment and for at least 12 hours after administration of this medicinal product.

4.7 Effects on ability to drive and use machines
This precaution is not relevant to the use of cisatracurium. This medicinal product will always be used in combination with a general anaesthetic and therefore the usual precautions relating to performance of tasks following general anaesthesia apply.

4.8 Undesirable effects
Data from pooled internal clinical trials were used to determine the frequency of very common to uncommon adverse reactions.

Within each system organ class, the adverse drug reactions are ranked under the headings of reporting frequency, using the following convention:

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)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
<td>Anaphylactic reaction</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very rare</td>
<td>Myopathy, Muscle weakness</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Uncommon</td>
<td>Rash</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Cutaneous flushing</td>
</tr>
</tbody>
</table>

Anaphylactic reactions of varying degrees of severity have been observed after the administration of neuromuscular blocking agents. Very rarely, severe anaphylactic reactions have been reported in patients receiving cisatracurium in conjunction with one or more anaesthetic agents.

There have been some reports of muscle/weakness and/or myopathy following prolonged use of muscle relaxants in severely ill patients in the ICU. Most patients were receiving concomitant
corticosteroids. These events have been reported infrequently in association with cisatracurium and a causal relationship has not been established.

4.9 Overdose
Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage with this medicinal product.

Management
It is essential to maintain pulmonary ventilation and arterial oxygenation until adequate spontaneous respiration returns. Full sedation will be required since consciousness is not impaired by this medicinal product. Recovery may be accelerated by the administration of anti-cholinesterase agents once evidence of spontaneous recovery is present.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Cisatracurium is a neuromuscular blocking agent, ATC code: M03A C11: muscle relaxants, peripherally acting agents; other quaternary ammonium compounds.

Cisatracurium is an intermediate-duration, non-depolarising benzylisoquinolinium skeletal muscle relaxant.

Clinical studies in man indicated that this medicinal product is not associated with dose dependent histamine release even at doses up to and including 8 x ED$_{95}$.

Mode of action
Cisatracurium binds to cholinergic receptors on the motor end-plate to antagonise the action of acetylcholine, resulting in a competitive block of neuromuscular transmission. This action is readily reversed by anti-cholinesterase agents such as neostigmine or edrophonium.

The ED$_{95}$ (dose required to produce 95% depression of the twitch response of the adductor pollicis muscle to stimulation of the ulnar nerve) of cisatracurium is estimated to be 0.05 mg/kg bodyweight during opioid anaesthesia (thiopentone/fentanyl/midazolam).

The ED$_{95}$ of cisatracurium in children during halothane anaesthesia is 0.04 mg/kg.

5.2 Pharmacokinetic properties
Cisatracurium undergoes degradation in the body at physiological pH and temperature by Hofmann elimination (a chemical process) to form laudanosine and the monoquaternary acrylate metabolite. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite. Elimination of cisatracurium is largely organ independent but the liver and kidneys are primary pathways for the clearance of its metabolites.

These metabolites do not possess neuromuscular blocking activity.

Pharmacokinetics in adult patients
Non-compartmental pharmacokinetics of cisatracurium are independent of dose in the range studied (0.1 to 0.2 mg/kg, i.e. 2 to 4 x ED$_{95}$).

Population pharmacokinetic modelling confirms and extends these findings up to 0.4 mg/kg (8 x ED$_{95}$). Pharmacokinetic parameters after doses of 0.1 and 0.2 mg/kg cisatracurium administered to healthy adult surgical patients are summarised in the table below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range of Mean Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>4.7 to 5.7 ml/min/kg</td>
</tr>
<tr>
<td>Volume of distribution at steady state</td>
<td>121 to 161 ml/kg</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>22 to 29 min</td>
</tr>
</tbody>
</table>

Pharmacokinetics in elderly patients
There are no clinically important differences in the pharmacokinetics of cisatracurium in elderly and young adult patients. The recovery profile is also unchanged.

**Pharmacokinetics in patients with renal/hepatic impairment**
There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage renal failure or end stage liver disease and in healthy adult patients. Their recovery profiles are also unchanged.

**Pharmacokinetics during infusions**
The pharmacokinetics of cisatracurium after infusions is similar to those after single bolus injection. The recovery profile after infusion of cisatracurium is independent of duration of infusion and is similar to that after single bolus injection.

**Pharmacokinetics in Intensive Care Unit (ICU) patients**
The pharmacokinetics of cisatracurium in ICU patients receiving prolonged infusions are similar to those in healthy surgical adults receiving infusions or single bolus injections. The recovery profile after infusions of this medicinal product in ICU patients is independent of duration of infusion. Concentrations of metabolites are higher in ICU patients with abnormal renal and/or hepatic function (see section 4.4). These metabolites do not contribute to neuromuscular block.

### 5.3 Preclinical safety data

**Acute toxicity**
Meaningful acute studies with cisatracurium could not be performed.

For symptoms of toxicity see “Overdosage”

**Subacute Toxicity**
Studies with repeated administration for three weeks in dogs and monkeys showed no compound specific toxic signs.

**Mutagenicity**
Cisatracurium was not mutagenic in an in vitro microbial mutagenicity test at concentrations up to 5000 μg/plate.
In an in vivo cytogenetic study in rats, no significant chromosomal abnormalities were seen at s.c. doses up to 4 mg/kg.

Cisatracurium was mutagenic in an in vitro mouse lymphoma cell mutagenicity assay, at concentrations of 40 μg/ml and higher.

A single positive mutagenic response for a drug used infrequently and/or briefly is of questionable clinical relevance.

**Carcinogenicity**
Carcinogenicity studies have not been performed.

**Reproductive toxicology**
Fertility studies have not been performed. Reproductive studies in rats have not revealed any adverse effects of cisatracurium on foetal development.

**Local tolerance**
The result of an intra-arterial study in rabbits showed that cisatracurium injection is well tolerated and no drug related changes were seen.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
- Benzenesulfonic acid (for pH adjustment)
- Water for Injections

#### 6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Since cisatracurium is stable only in acidic solutions it should not be mixed in the same syringe or administered simultaneously through the same needle with alkaline solutions, e.g., sodium thiopentone. It is not compatible with ketorolac, trometamol or propofol injectable emulsion.

6.3 Shelf life
As packaged for sale: 18 months.
Shelf life after dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 5°C and 25°C at concentrations of 0.1 and 2 mg/ml in PVC infusion bags.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C). Do not freeze. Keep vials in the outer carton in order to protect from light.

For storage conditions for the diluted solution, see section 6.3.

6.5 Nature and contents of container
Clear Type I glass vials with rubber stopper; packs of 1 and 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
This product is for single use only.

Use only clear and almost colourless up to slightly yellow/greenish yellow coloured solutions. The product should be visually inspected before use, and if the visual appearance differs from the above description or if the container is damaged, the product must be discarded.

This medicinal product may be diluted to concentrations between 0.1 and 2 mg/ml with the following infusion solutions:
- Sodium Chloride (0.9% w/v) IV Infusion
- Glucose (5% w/v) IV Infusion
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) IV infusion
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) IV infusion

Since the product contains no antimicrobial preservative, dilution should be carried out immediately prior to use, or failing this, the diluted solution should be stored as directed in section 6.3.

Cisatracurium has been shown to be compatible with the following commonly used peri-operative drugs, when mixed in conditions simulating administration into a running intravenous infusion via a Y-site injection port: alfentanil hydrochloride, droperidol, fentanyl citrate, midazolam hydrochloride and sufentanil citrate. Where other drugs are administered through the same indwelling needle or cannula as this medicinal product, it is recommended that each drug be flushed through with an adequate volume of a suitable intravenous fluid, e.g., sodium chloride intravenous infusion (0.9% w/v).

As with other drugs administered intravenously, when a small vein is selected as the injection site, cisatracurium should be flushed through the vein with a suitable intravenous fluid, e.g., sodium chloride intravenous infusion (0.9% w/v).

7 MARKETING AUTHORISATION HOLDER
Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
PL 04515/0234
PL 04515/0235

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/10/2011

10 DATE OF REVISION OF THE TEXT
20/10/2011
Module 3
Product Information Leaflet

PAR Cisatracurium 2mg/mL and 5 mg/mL Solution for injection/infusion

16

Hospira

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Cisatracurium 2 mg/ml
Solution for Injection/Infusion

Cisatracurium 5 mg/ml
Solution for Injection/Infusion

Cisatracurium

Read all of this leaflet carefully before you start using this medicine
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet
1. What Cisatracurium is and what it is used for
2. Before you are given Cisatracurium
3. How you are given Cisatracurium
4. Possible side effects
5. How to store Cisatracurium
6. Further information

1. WHAT CISATRACURUM IS AND WHAT IT IS USED FOR

Cisatracurium belongs to a group of medicines called muscle relaxants. The full name of this medicine is Cisatracurium Solution for Injection/Infusion but for ease of reference it will be referred to as Cisatracurium throughout the leaflet.

Cisatracurium is used
• during surgery and other procedures and in intensive care
• with general anaesthesia, or sedation in the Intensive Care Unit to relax muscles
• to help insert a tube into the windpipe (tracheal intubation) if a person needs help to breathe (with or without a machine).

Cisatracurium is used in adults and in children over 1 month of age.

2. BEFORE YOU ARE GIVEN CISATRACURUM

You will not be given Cisatracurium
• If you are allergic (hypersensitive) to cisatracurium besilate, atracurium or any of the other ingredients in this medicine (see section 6).

Take special care with Cisatracurium
Speak with your doctor before receiving this medicine if you:
• have a neuromuscular disease, such as a muscle wasting disease, paralysis, motor neurone disease, cerebral palsy or myasthenia gravis
• have a burn which requires medical treatment
• have ever had an allergic reaction to any muscle relaxant
• are aware that you have abnormal blood acidity or abnormal blood electrolyte levels

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This includes herbal medicines. This is because these medicines can affect how well Cisatracurium works or cause side effects.

In particular tell your doctor, nurse or pharmacist if you are taking, or have recently received any of the following:
• anaesthetics (used to reduce sensation and pain during surgical procedures)
• antibiotics (used to treat infections)
• medicines for uneven heart beats (anti-arrhythmics)
• medicines for high blood pressure
• water tablets (diuretics), such as frusemide
• medicines for inflammation of the joints, such as chloroquine or d-penicillamine
• steroids
• medicines for fits (epilepsy), such as phenytoin or carbamazepine
• medicines for mental illness, such as lithium, monoamine oxidase inhibitors (MAOIs) or chlorpromazine (which can also be used for nausea)
• medicines containing magnesium
• medicines for Alzheimer’s disease (anticholinesterases such as donepezil)
• other muscle relaxants

Pregnancy and breastfeeding
You should not be given this medicine if you are pregnant. If you are pregnant and you are given this medicine because of a medical emergency, ask your doctor for advice before starting breastfeeding again. Breastfeeding may be started 24 hours after this medicine has been given to you.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Some patients may occasionally feel dizzy, drowsy or confused after treatment with this medicine. If this happens to you, do not drive or use machinery. Your doctor will advise how long you should wait after an operation before you can drive.
3. HOW YOU ARE GIVEN CISATRACURIUM

Cisatracurium will be administered to you by a healthcare professional

This medicine will only be administered directly into a vein, either by injection or by slow intravenous infusion. Cisatracurium can be given as a single injection into your vein (intravenous bolus injection) or as a continuous infusion into your vein. This is where the drug is slowly given to you over a longer period of time.

Your doctor will decide how you will be given this medicine and the dose you will receive. This depends on the following factors:

- your body weight
- the amount and duration of muscle relaxation required
- your expected response to the medicine.

Use in Children

Children less than 1 month old should not be given this medicine.

If you receive more Cisatracurium than you should

This medicine will always be given to you by your doctor or anaesthetist under carefully controlled conditions. It is unlikely that you will be given too much, however, tell your doctor or nurse if you have any concerns.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The assessment of the side effects is based on the following frequencies:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data

The following side effects have been reported following the administration of this medicine:

Common

- decreased heart rate
- low blood pressure

Uncommon

- a rash or redness on your skin
- coughing or wheezing

Very rare

- muscle wasting and muscle weakness
- severe allergic reactions

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CISATRACURIUM

Keep out of the reach and sight of children.

Do not use this medicine after the expiry date, which is stated on the carton and the label. The expiry date refers to the last day of that month.

Store in a refrigerator between 2 - 8°C. Do not freeze. Keep the vial in the outer carton in order to protect from light.

To be used only if the solution appears clear and almost colourless to slightly yellow/greenish coloured. The product should be visually inspected before use, and if the visual appearance differs from the above description or if the container is damaged, the product must be discarded.

Unused portions of opened vials must not be stored for later use.

Diluted solutions should be used immediately, however, if this is not possible they can, in certain circumstances, be stored for up to 24 hours.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cisatracurium contains

- The active substance is cisatracurium besilate.
  - Each 2.5 ml vial contains 5 mg cisatracurium (as cisatracurium besilate)
  - Each 5 ml vial contains 10 mg cisatracurium (as cisatracurium besilate)
  - Each 10 ml vial contains 20 mg cisatracurium (as cisatracurium besilate)
  - Each 30 ml vial contains 150 mg cisatracurium (as cisatracurium besilate)
- The other ingredients are benzencesulfonic acid and Water for Injections.

What this medicine looks like and the contents of the pack

Cisatracurium is a colourless to pale yellow/greenish solution which comes in glass containers called vials. This medicine may be supplied in packs containing 1 or 5 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
UK

Manufacturers responsible for batch release

Hospira Spa
Via Fosse Ardeatine, 2
20060 Liscate (MI)
Italy

This leaflet was last approved in: 10/2011
Cisatracurium 2 mg/ml
Solution for Injection/Infusion

Cisatracurium 5 mg/ml
Solution for Injection/Infusion

The following information is intended for medical or healthcare professionals only.

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in 'Instructions for use and handling' below.

Since cisatracurium is stable only in acidic solutions it should not be mixed in the same syringe or administered simultaneously through the same needle with alkaline solutions, e.g., sodium thiopentone. It is not compatible with ketorolac, tramadol or propofol injectable emulsion.

Instructions for use and handling

For single use only.

Use only clear and almost colourless up to slightly yellow/greenish yellow coloured solutions. The product should be visually inspected before use, and if the visual appearance has changed or if the container is damaged, the product must be discarded.

The diluted product is stable for at least 24 hours at concentrations between 0.1 – 2.0 mg/ml in the following infusion solutions:
- Sodium Chloride (0.9% w/v) IV infusion
- Glucose (5% w/v) IV infusion
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) IV infusion
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) IV infusion

However, since the product contains no antimicrobial preservative, dilution should be carried out immediately prior to use, or failing this the diluted solution should be stored as directed below.

Cisatracurium has been shown to be compatible with the following commonly used peri-operative drugs, when mixed in conditions simulating administration into a running intravenous infusion via a Y-site injection port: alfentanil hydrochloride, dexamethasone, fentanyl citrate, midazolam hydrochloride and sufentanil citrate. Where other drugs are administered through the same indwelling needle or cannula as this medicinal product, it is recommended that each drug be flushed through with an adequate volume of a suitable intravenous fluid, e.g., Sodium Chloride Intravenous Infusion (0.9% w/v).

As with other drugs administered intravenously, when a small vein is selected as the injection site, cisatracurium should be flushed through the vein with a suitable intravenous fluid, e.g., sodium chloride intravenous infusion (0.9% w/v).

Shelf life after dilution

Shelf life after dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 5°C and 25°C at concentrations of 0.1 and 2 mg/ml in PVC infusion bags.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
Module 4
Labelling

Carton

Cisatracurium 2 mg/ml and 5 mg/ml Solution for injection/infusion

Module 4
Labelling

Carton

Cisatracurium

2 mg/ml
Solution for Injection/Infusion
cisatracurium bisulfate

5 mg / 2.5 ml
For intravenous use
Read the package leaflet before use

Store in a refrigerator.
Do not freeze. Keep vials in the outer carton in order to protect from light.
Keep out of the reach and sight of children.
Cisatracurium 2 mg/mL and 5 mg/mL Solution for injection/infusion

10 mg / 5 ml

For Intravenous use

Read the package leaflet before use

Store in a refrigerator.
Do not freeze. Keep inside the outer carton in order to protect from light.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION

On 22 August 2011, Austria, Belgium, Cyprus, Czech Republic, Denmark, Germany, Estonia, France, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Slovakia, Spain and the UK agreed to grant Marketing Authorisations (MAs) to Hospira UK Limited for the medicinal products Cisatracurium 2 mg/ml and 5 mg/mL Solution for Injection/Infusion. The MAs were granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (UK/H/3758/001-002/DC). After the national phase, licences were granted in the UK on 20 October 2011 (PL 04515/0234-5).

These are generic applications for Cisatracurium 2 mg/ml and 5 mg/mL Solution for Injection/Infusion, submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applications refer to Nimbrex 2 mg/mL and 5 mg/mL Solution for Injection (PL 00003/0364-5), first authorised to The Wellcome Foundation in the UK on 7 August 1995. The period of exclusivity has expired.

Cisatracurium is an intermediate-duration, non-depolarising neuromuscular blocking agent. Cisatracurium binds to cholinergic receptors on the motor end-plate to antagonise the action of acetylcholine, resulting in a competitive block of neuromuscular transmission. This action is readily reversed by anti-cholinesterase agents such as neostigmine or edrophonium. Cisatracurium is indicated for use during surgical and other procedures and in intensive care. Cisatracurium can be used as an adjunct to general anaesthesia, or sedation in the Intensive Care Unit (ICU) to relax skeletal muscles and to facilitate tracheal intubation and mechanical ventilation. Cisatracurium is generally well tolerated. Common adverse events include bradycardia and hypotension.

The R-cis isomer of atracurium besilate is approximately 3-fold more potent than the mixture of isomers that constitute the parent drug. Cisatracurium undergoes degradation in the body at physiological pH and temperature by Hofmann elimination to form laudanosine and the monoquaternary acrylate metabolite. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite. Elimination of cisatracurium is largely organ independent but the liver and kidneys are primary pathways for the clearance of its metabolites. There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage renal failure or end stage liver disease compared with healthy adult patients or between elderly and young adult patients.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years. Bioequivalence studies were not necessary to support these applications for aqueous parenteral products.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. 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 authorities 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 in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active substance is well established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that the marketing of this product will change the overall use pattern of the existing market.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Cisatracurium 2 mg/ml Solution for Injection/Infusion  
Cisatracurium 5 mg/ml Solution for Injection/Infusion |
| Name(s) of the active substance(s) (INN) | Cisatracurium Besilate |
| Pharmacotherapeutic classification (ATC code) | Neuromuscular blocking agent  
ATC code: M03A C11 |
| Pharmaceutical form and strength(s) | Solution for Injection/Infusion  
2 mg/ml & 5 mg/ml |
| Reference numbers for the Decentralised Procedure | UK/H/3758/01-02/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Austria, Belgium, Cyrpus, Czech Republic, Denmark, Germany, Estonia, France, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Slovakia and Spain. |
| Marketing Authorisation Number(s) | PL 04515/0234-5 |
| Name and address of the authorisation holder | Hospira UK Limited  
Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, UK |
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

DRUG SUBSTANCE
Cisatracurium besilate
INN: Cisatracurium besilate

Chemical name: 
(1R,1'R,2R,2R')-2,2'-[1,5-pentanediilbis[oxy(3-oxo-3,1-propanediyl)]bis[1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolinium] dibenzenesulfonate

Structure:

![Structure of Cisatracurium besilate](image)

Molecular formula: C_{65}H_{82}N_{2}O_{18}S_{2}

Molecular weight: 1243.5

General Properties
Description:
Cisatracurium besilate is a hygroscopic, white to yellowish powder.

Solubility:
Sparingly soluble in water.

Cisatracurium besilate is not currently the subject of a European Pharmacopoeia (Eur Ph.) monograph.

Manufacture
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.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**DRUG PRODUCT**

**Description and Composition**

Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion is presented as a colourless to pale yellow or greenish yellow solution.

Cisatracurium 2 mg as cisatracurium besilate 2.7 mg per 1 ml and Cisatracurium 5 mg as cisatracurium besilate 6.7 mg per 1 ml.

**Other ingredients**

Other ingredients consist of the pharmaceutical excipients, benzenesulfonic acid (for pH adjustment) and water for injections. Water for injections shows compliance with its Ph Eur monograph and benzenesulfonic acid complies with an in-house specification which is satisfactory.

Appropriate justification for the inclusion of each of the excipients has been provided. Satisfactory Certificates of Analysis for each of the excipients have been presented. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in the product, or used in the manufacturing process. Furthermore, no genetically modified organisms are used in the manufacture of the excipients.

**Pharmaceutical Development**

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop a stable, robust, generic dosage form of Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion, which is pharmaceutically equivalent to the reference product Nimbex 2 mg/mL and 5 mg/mL Solution for Injection (The Wellcome Foundation Limited).

Comparative impurity data were provided for batches of the test and reference products. The impurity profiles were satisfactory.

**Manufacture**

A description and flow-chart of the manufacturing method were provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted on sufficient batches of the product; the results were satisfactory. The validation data demonstrated consistency of the manufacturing process.

**Finished Product Specification**

Finished product specifications are provided for both release and shelf–life, and are satisfactory. These 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 adequately validated, as appropriate. Batch data are provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container Closure System**
The finished product is licensed for marketing in Type I glass vials with rubber stoppers. The glass vials are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of either 1 or 5 glass vials.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs. The glass vials comply with Ph Eur requirements and are suitable for contact with solutions for infusion/injection.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 18 months has been set, when the bottle is unopened, which is satisfactory. The storage conditions are ‘Store in a refrigerator (2°C-8°C). Do not freeze. Keep vials in the outer carton in the order to protect from light’.

An ‘in-use’ product stability study was carried out on one batch of Cisatracurium 2 mg/mL Solution for Injection/Infusion to establish the time period over which the product could be used after the vial has been opened. Chemical and physical in-use stability has been demonstrated for 24 hours at 5°C and 25°C at concentrations of 0.1 and 2 mg/ml in PVC infusion bags.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

**Compatibility Studies**
The compatibility studies were carried out on one batch of Cisatracurium 2 mg/mL Solution for Injection/Infusion and diluted to concentrations between 0.1 and 2 mg/ml with the following infusion solutions:
- Sodium Chloride (0.9% w/v) IV Infusion
- Glucose (5% w/v) IV Infusion
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) IV infusion
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) IV infusion

Since the product contains no antimicrobial preservative, dilution should be carried out immediately prior to use, or failing this, the diluted solution should be stored as directed in section 6.3 of the SmPC.

**Quality Overall Summary**
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are acceptable from a pharmaceutical perspective. The labelling is satisfactory and fulfils the statutory requirements for Braille. Mock-ups of the PIL and labelling have been provided. The PIL user-testing report has been evaluated and is acceptable.

MAA Form
The MAA forms are satisfactory from a pharmaceutical perspective.

Conclusion
The test products have been demonstrated to be equivalent pharmaceutically to the reference products, which have been licensed in the UK for over 10 years.

There are no objections to the approval of Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
Pharmacodynamic, pharmacokinetic and toxicological properties of cisatracurium besilate are well known. As this is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

Environmental risk assessment
No formal Environmental Risk Assessment has been provided. The applicant has justified the absence adequately. As a generic product, the use of this product is not expected to increase the overall use of cisatracurium besilate and so no additional increase in environmental risk has been identified.

Non-Clinical Overview
The non-clinical overview was written by a suitably qualified person and is satisfactory. The curriculum vitae of the expert has been provided.

Summary of Product Characteristics (SmPC)
Section 4.6 and 5.3 are satisfactory from a non-clinical viewpoint.

There are no objections to approval of Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS
Cisatracurium is indicated for use during surgical and other procedures and in intensive care in adults and children aged 1 month and over. It can be used as an adjunct to general anaesthesia, or sedation in the Intensive Care Unit (ICU) to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation.

The indications are consistent with those for the reference products and are satisfactory.
POSOLOGY AND METHOD OF ADMINISTRATION
Cisatracurium should only be administered by or under the supervision of anaesthetists or other clinicians who are familiar with the use and action of neuromuscular blocking agents. Facilities for tracheal intubation and maintenance of pulmonary ventilation and adequate arterial oxygenation have to be available.

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY
The toxicology of cisatracurium besilate is well-known. No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY
The clinical pharmacology of cisatracurium besilate is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

CLINICAL EFFICACY
No new data are submitted and none are required. Efficacy is reviewed in the clinical overview. The efficacy of cisatracurium besilate is well-established from its extensive use in clinical practice.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product (CPMP/QWP/EWP/1401/98, Parenteral solutions). These conditions have been met and the biowaiver is accepted; the applicant is not required to submit a bioequivalence study.

CLINICAL SAFETY
No new safety data have been submitted and none are required for application of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of cisatracurium besilate is well-known.

Expert Report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The curriculum vitae of the expert has been provided.

PRODUCT INFORMATION
Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those of the UK reference products and are acceptable.

Patient Information Leaflet (PIL)
The final PIL is in line with the approved SmPCs and is satisfactory. The PIL user-testing has been evaluated and is accepted.

Labelling
The labelling text is satisfactory.
Clinical overview
A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

MAA form
The MAA form is satisfactory.

Conclusion
There are no objections to the approval of Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion are 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
The applicant’s Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion products have been demonstrated to be generic versions of the reference products, Nimbrex 2 mg/mL and 5 mg/mL Solution for Injection (PL 00003/0364-5); The Wellcome Foundation. Bioequivalence studies are not necessary to support these applications for a solution for injection/infusion.

No new or unexpected safety concerns arose from these applications.

PRODUCT LITERATURE
The SmPC and PIL are acceptable and consistent with those for the reference product. The labelling is acceptable and in line with current requirements.

A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC (as amended). The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling text is satisfactory and fulfils the statutory requirements for Braille.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Cisatracurium 2 mg/mL and 5 mg/mL Solution for Injection/Infusion products are generic versions of the reference products Nimbrex 2 mg/mL and 5 mg/mL Solution for Injection (The Wellcome Foundation). Extensive clinical experience with cisatracurium besilate is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk ratio is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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