Public Assessment Report

Decentralised Procedure

Cisatracurium 2mg/ml solution for injection/infusion

Procedure No: UK/H/4276/001/DC

UK Licence No: PL 24598/0031

Noridem Enterprises Limited
LAY SUMMARY

On 02 July 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Noridem Enterprises Limited for the medicinal product Cisatracurium 2mg/ml solution for injection/infusion (PL 24598/0031; UK/H/4276/001/DC). This is prescription-only medicine (POM) used to:

- relax muscles during operations on adults and children over 1 month of age, including heart surgery
- help insert a tube into the windpipe (tracheal intubation), if a person needs help to breathe
- relax the muscles of adults in intensive care.

Cisatracurium 2mg/ml solution for injection/infusion contains the active ingredient cisatracurium (as cisatracurium besilate), which belongs to a group of medicines called muscle relaxants.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Cisatracurium 2mg/ml solution for injection/infusion outweigh the risks and a Marketing Authorisation was granted.
TABLE OF CONTENTS

Module 1: Information about the initial procedure  Page 4

Module 2: Summary of Product Characteristics  Page 5

Module 3: Patient Information Leaflet  Page 6

Module 4: Labelling  Page 7

Module 5: Scientific discussion during initial procedure  Page 13
   I Introduction
   II About the product
   III Scientific overview and discussion
   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  Page 19
# Module 1

## Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name(s)</th>
<th>Cisatracurium 2mg/ml solution for injection/infusion</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
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<tr>
<td>Active Substance(s)</td>
<td>Cisatracurium besilate</td>
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<tr>
<td>Form</td>
<td>Solution for injection/infusion</td>
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<tr>
<td>Strength</td>
<td>2 mg/ml</td>
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<td>MA Holder</td>
<td>Noridem Enterprises Ltd</td>
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<td></td>
<td>Evagorou &amp; Makariou,</td>
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<tr>
<td></td>
<td>Mitsi Building 3</td>
</tr>
<tr>
<td></td>
<td>Office 115, 1065 Nicosia, Cyprus</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>Austria, Germany, Greece, Spain, Ireland and Poland</td>
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<td>Procedure Number(s)</td>
<td>UK/H/4276/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 02 June 2013</td>
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Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Cisatracurium 2mg/ml solution for injection/infusion

For intravenous use only

Cisatracurium
One ml contains Cisatracurium Besylate corresponding to 2mg Cisatracurium.
One 5ml ampoule contains 10ml of Cisatracurium. It also contains benzyl alcohol (2.5% w/v), sodium chlorate and sodium hydroxide or hydrochloric acid for adjustment of pH to 6.5 to 7.0.

Store in a refrigerator (2°C to 8°C). Do Not Freeze.

Store in the original packaging in order to protect from light. Read the leaflet for the shelf life of the diluted product. Single use only. Discard the remaining contents of the ampoule after use. Use only clear solutions. Do not use if discolouration or precipitation is observed.

Keep out of the sight and reach of children.

Manufactured by:
DEMO S.A.
PHARMACEUTICAL INDUSTRY
27th Eka Mino, Larnaca, 146-68 Athens, Greece.

Marketing Authorisation Holder:
noridem
ENTREPRISES LTD
Porongos, Kato Makedonias, Mt Μοιρα, Συγελα, 1101 Nicosia, Cyprus.

LOT: XXXX
EXP: MMMYY

Cisatracurium 2mg/ml solution for injection/infusion

For intravenous use only

10mg/5ml

5 ampoules x 5ml
Cisatracurium 2mg/ml solution for injection/infusion

Cisatracurium

1 ampoule x 10ml

Manufactured by:
DEMO S.A.
FARMACEUTICAL INDUSTRY
31, Konstantinou - Larissa, 531 00 Aristotelous, Greece

Marketing Authorisation Holder
nordem®
ENTRANOS LTD
Everyday Market, Mitie Building, 3rd Floor, 1055 Nicosia, Cyprus

UK: PL 24889/001
SG P11280/001
POM

Lot: XXXXXXX
Exp: MM/YYYY

104 x 26 x 55mm

BLACK

PMS 7462 C
Cisatracurium 2mg/ml solution for injection/infusion

For intravenous use only

Cisatracurium 2mg/ml solution for injection/infusion

5 ampoules x 10ml

Manufactured by:
DEMO S.A.
PHARMACEUTICAL INDUSTRY
DEMOS S.A. 11th km Athens - Larisa, 146 80 Athens, Greece

Marketing Authorisation Holder:
Noridem ENTERPRISES LIMITED
Stenonos & Maroulou, Nike Doulou, 3, Sinti, 3 188 Neos, Cyprus.

Cisatracurium 2mg/ml solution for injection/infusion

5 ampoules x 10ml

For intravenous use only

LOT: XXXXXX
EXP: MAMMYY
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Cisatracurium 2mg/ml solution for injection/infusion (PL 24598/0031; UK/H/4276/001/DC) could be approved. The product is a prescription-only medicine (POM).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Germany, Greece, Spain, Ireland and Poland as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Nimbex 2 mg/ml solution for injection/infusion (authorised to The Wellcome Foundation Limited, UK, trading as GlaxoSmithKline UK) which was approved in the UK on 07 August 1995.

The active ingredient, cisatracurium (as cisatracurium besilate), 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 intravenous administration, for use during surgical and other procedures and in intensive care in adults and children aged 1 month and over. 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.

No new non-clinical or clinical studies were performed, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years. A bioequivalence study was not necessary to support this application for a parenteral product (aqueous solution).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. 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.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 02 June 2013. After a subsequent national phase, a licence was granted in the UK on 02 July 2013.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Cisatracurium 2mg/ml solution for injection/infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Cisatracurium besilate</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Neuromuscular blocking agent (ATC code: M03A C11)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Solution for injection/infusion</td>
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<tr>
<td>Reference number for the Decentralised Procedure</td>
<td>UK/H/4276/001/DC</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>Austria, Germany, Greece, Spain, Ireland and Poland</td>
</tr>
<tr>
<td>Marketing Authorisation Numbers</td>
<td>PL 24598/0031</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Noridem Enterprises Ltd Evagorou &amp; Makariou, Mitsi Building 3 Office 115, 1065 Nicosia, Cyprus</td>
</tr>
</tbody>
</table>

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Cisatracurium besilate
Chemical Name: (1R,1'R,2R,2'R')-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
Molecular formula: C_{65}H_{82}N_{2}O_{18}S_{2}
Structure:

![Structure Diagram]

Molecular mass: 1243.5
Appearance: Amorphous white to off white powder
Solubility: Sparingly soluble in water and soluble in acidic solution.

Cisatracurium besilate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been described adequately 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. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been validated appropriately and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.
Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

**MEDICINAL PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients benzene sulfonic acid solution 32 % w/v (for pH adjustment) and Water for injections. Appropriate justification for the inclusion of each excipient has been provided.

Water for injections complies with its European Pharmacopoeia monograph. Benzene sulfonic acid solution 32 % w/v complies with a suitable in-house specification. Certificates of Analysis have been provided for both excipients, showing compliance with the proposed specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to produce a stable formulation of cisatracurium (as cisatracurium besilate) in a 2 mg/ml solution for injection/infusion comparable in performance to the reference product Nimbex 2 mg/ml solution for injection/infusion (The Wellcome Foundation Limited, trading as GlaxoSmithKline UK, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for this product and the reference product.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches and has shown satisfactory results.

**Control of Finished Product**

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been 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 supplied in 2.5 ml, 5 ml and 10 ml type I clear, neutral glass ampoules, packed in cardboard outer cartons in pack sizes of 1 and 5 ampoules.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidance concerning materials in contact with parenteral products.
Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been approved for the undiluted product, with the storage conditions “Store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original package in order to protect from light”.

It is stated that 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 and would normally not be longer than 24 hours at 2 to 8°C.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this application for this aqueous solution, parenteral product.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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 the leaflet contains.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of cisatracurium besilate are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS

Clinical Pharmacology
No new clinical pharmacology data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for an aqueous parenteral product. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1, Guideline on the Investigation of Bioequivalence).

Efficacy
No new efficacy data have been submitted and none are required for this type of application.

Safety
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application. As an active ingredient, cisatracurium besilate has a well-established safety profile and an acceptable level of safety in the proposed indications.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the innovator product. The PIL is consistent with the details in the SmPC and in line with the current guidance. The labelling is in line with the current guidance.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
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.

Suitable justification has been provided for not submitting a Risk Management Plan for this application.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Cisatracurium 2mg/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 this type of application.

EFFICACY
No new clinical data were submitted for this application. No bioequivalence studies were submitted or required for this application.

SAFETY
No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant’s product and the reference product are interchangeable. Extensive clinical experience with cisatracurium besilate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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