IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Cisatracurium 2 mg/ml solution for injection/infusion
Cisatracurium
PA1122/017/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/4276/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 10th October 2018 under procedure number IE/H/0712/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1122/017/001
Marketing Authorisation Holder: Noridem Enterprises Ltd.

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

Product Name(s)	Cisatracurium 2mg/ml solution for injection/infusion
Type of Application	Generic, Article 10(1)
Active Substance(s)	Cisatracurium besilate
Form	Solution for injection/infusion
Strength	2 mg/ml
Pharmacotherapeutic classification (ATC code)	M03A C11 - neuromuscular blocking agent
Marketing Authorisation Number in Ireland	PA1122/017/001
MA Holder	Noridem Enterprises Ltd Evagorou & Makariou, Mitsi Building 3 Office 115, 1065 Nicosia, Cyprus

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 2001183/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.

In a repeat use procedure (IE/H/0712/001/E/001) authorisation was further extended to CMS's FR, IT, ES, CZ, SK, SE, DK, NO, FI, NL HU, RO, PT, CY.

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.

II. QUALITY ASPECTS

ACTIVE SUBSTANCE

The active substance is cisatracurium besilate an established active substance described in the European Pharmacopoeia and it is manufactured in accordance with the principles of Good Manufacturing Practice.

The active substance specification is considered adequate to control the quality requirements. Batch analytical data demonstrating compliance with this specification has been provided.

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.

Conclusion
The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Cisatracurium 2mg/ml solution for injection/infusion.

III. 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.

IV. CLINICAL ASPECTS

Clinical Pharmacololgy
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. 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.

The Marketing Authorisation Holder (MAH) has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cisatracurium 2 mg/ml solution for injection/infusion.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

• PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
• For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
• In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Conclusion
The grant of a Marketing Authorisation is recommended.

V. OVERALL CONCLUSIONS

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.

VI. REVISION DATE

October 2025

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/4276/001/DC to IE/H/0712/001/DC	N/A	N/A	N/A	Approved 10/10/2018