Decentralised Procedure

Public Assessment Report

Cisatracurium HEXAL 2 mg/ml
Injektionslösung/Infusionslösung

Cisatracurium besilate

DE/H/2770/001/DC

Applicant:
Hexal AG

| Reference Member State | DE |
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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Cisatracurium HEXAL 2 mg/ml solution for injection /infusion in the use as an adjunct to general anaesthesia during surgical and other procedures, or sedation in the Intensive Care Unit (ICU) to relax skeletal muscles, and to facilitate endotracheal intubation and mechanical ventilation in adults and children aged 1 month and over is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

For generic application this section is not applicable.

II.2 About the product

Cisatracurium besilate is a nondepolarizing skeletal muscle relaxant for intravenous administration. Compared to other neuromuscular blocking agents, it is intermediate in its onset and duration of action. Cisatracurium besilate is the 1R-cis 1'R-cis isomer of atracurium and 3 times more potent than atracurium. At equipotent doses, cisatracurium has a slower onset of action but a similar duration of effect to atracurium. Cisatracurium exhibits less histamine release compared to atracurium and is characterised by a remarkable haemodynamic stability.

The claimed indications for Cisatracurium HEXAL 2 mg/ml solution for injection /infusion are identical with the indications of the originator product (Nimbex®):

Cisatracurium besilate is indicated for use during surgical and other procedures and in intensive care. 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 SmPC is in line with the originator’s SmPC.

II.3 General comments on the submitted dossier

This marketing authorisation application is an abridged application, according to article 10.2(b) so called “generic application”.

In this Decentralised Procedure Hexal AG, Germany is applying for the Marketing Authorisations for Cisatracurium HEXAL 2 mg/ml solution for injection /infusion in BE, ES, FR, IT with Germany as the Reference Member State. The originator product is Nimbex 2 mg/ml solution for injection by GlaxoSmithKline GmbH & Co. KG, registered since 1996-02-13.

The applicant did not perform any bioequivalence studies. According to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, bioequivalence studies are not required as the product is an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized product.

For generic applications a paediatric development program is not applicable.

The submitted dossier is in general of acceptable quality.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug Substance

The active substance of Cisatracurium 2 mg/ml Solution for Injection or Infusion is Cisatracurium besilate. Cisatracurium besilate is an intermediate-duration, non-depolarising neuromuscular blocking agent. Cisatracurium is not covered by a monograph of the European Pharmacopoeia (Ph Eur). The manufacturers of the drug substance have applied an ASMF procedure for Cisatracurium besilate respectively. A letter of Access has been provided by both ASMF holders respectively.

The claimed re-test period of one year (stored under refrigerator conditions) is acceptable for the drug substance coming from manufacturer B. For the drug substance supplied by manufacturer A, the re-test period of 18 months is acceptable when stored in the freezer.

Drug Product

The aim of pharmaceutical development was to develop a generic drug product comparable to Nimbex® 2 mg/ml solution for injection manufactured by GlaxoSmithKline. The product developed has the same active substance, dosage form, strength, and route of administration and conditions of use as the reference product.

All relevant quality characteristics of the drug substance and the drug product (release and shelf-life) are specified.

The description of the analytical methods used to analyse the drug substance and drug product are adequate, the validation results are plausible.

Based on 18 months stability data, a shelf life of 18 months is accepted for the drug product when stored in the outer carton at 2-8°C.

III.2 Nonclinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Cisatracurium are well known. As Cisatracurium is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Since Cisatracurium HEXAL 2 mg/ml contains the same excipients, benzensulfonic acid 1 % and water as the reference product, there are no concerns regarding the composition of the final formulation.

The profile and specification limit of the impurities are acceptable from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics

Cisatracurium is degraded by Hofmann elimination to 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, which do not exhibit neuromuscular blocking activity. The recovery profile after infusion of cisatracurium is independent of dose and duration of infusion and is similar to that after single bolus injection. There are only minor differences in pharmacokinetics of cisatracurium besilate in patients with renal or hepatic failure or in elderly patients, not requiring dose adjustments.
**Pharmacodynamics**

Cisatracurium besilate is a non-depolarizing skeletal muscle relaxant for intravenous administration. Compared to other neuromuscular blocking agents, it is intermediate in its onset and duration of action. Cisatracurium besilate is the 1R-cis 1'R-cis isomer of atracurium and 3 times more potent than atracurium (ED95 for cisatracurium bis-cation is 0.05 mg/kg compared with atracurium besilate salt 0.23 mg/kg). At equipotent doses, cisatracurium has a slower onset of action but a similar duration of effect to atracurium.

**Clinical efficacy**

Cisatracurium besilate is indicated for use during surgical and other procedures and in intensive care. 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.

**Clinical safety**

Cisatracurium exhibits less histamine release compared to atracurium and is characterised by a remarkable haemodynamic stability.

**User Testing**

Overall, the test methodology follows the guidelines of the European Commission (*Guideline on the readability of the label and package leaflet of medicinal products for human use*, Revision January 2009; Update of Directive 2001/83/EC as amended by Directive 2004/27/EC / *Guidance concerning consultations with target patient groups for the packet leaflet*, May 2006). Directive 2001/83/EC as amended require that consultation with target patient groups are carried out to demonstrate the readability and usefulness of the package leaflet to patients. The applicant has included the results of consultation with target patient group in Module 1.3.4 of the application. The result of the consultation with target patient groups is regarded acceptable by the RMS.

**Pharmacovigilance system**

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant 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.

**Risk Management Plan**

Not required.

**IV. BENEFIT RISK ASSESSMENT**

Pharmacodynamic, pharmacokinetic and toxicological properties of Cisatracurium are well known. As Cisatracurium is a widely used, well-known active substance, no further studies are required and the applicant provides none. The provided overview based on literature review is appropriate.

The application is approved.