IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Amikacin 250 mg/ml Solution for injection/infusion
AMIKACIN SULFATE
PA1122/034/002

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

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Amikacin 250 mg/ml solution for injection/infusion from Noridem Enterprises Limited on 24th May 2024 for the short-term treatment of serious infection due to susceptible strains of bacteria when less toxic antimicrobial agents are not effective.

This application for a marketing authorisation was submitted via a decentralised procedure in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as an 'generic' application.

Ireland was the Reference Member State (RMS) and the Concerned Member States (CMSs) were Czech Republic, Greece, Spain, France, Hungary, Italy, Poland, Romania and Slovakia.

These are prescription-only medicinal products.

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

Name of the product	Amikacin 250mg/ml solution for injection/ infusion
Name(s) of the active substance(s) (INN)	AMIKACIN SULFATE
Pharmacotherapeutic classification (ATC code)	J01GB06
Pharmaceutical form and strength(s)	Solution for injection/ infusion 250mg/ml
Marketing Authorisation Number(s) in Ireland (PA)	PA1122/034/002
Marketing Authorisation Holder	Noridem Enterprises Limited, Evagorou & Makariou, Mitsi Building 3, Office 115, 1065 Nicosia, Cyprus
MRP/DCP No.	IE/H/1239/001-002/DC
Reference Member State	IE
Concerned Member State	CZ, EL, ES, FR, HU, IT, PL, RO, SK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Amikacin 125 mg/ml and 250 mg/ml solution for injection/infusion.

II.2 Drug substance

The active substance is amikacin sulfate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

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

II.3 Medicinal product

P.1 Composition

The medicinal products are solutions containing amikacin sulfate equivalent to 125 mg/ml and 250 mg/ml of amikacin.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for parenteral preparations and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Amikacin 125 mg/ml and 250 mg/ml solution for injection/infusion

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance, amikacin, is a generic formulation of Briklin (250 mg/2 ml and 500 mg/ 2 ml, solution for injection), on the European market since 1974. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of amikacin are well known. As amikacin is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

III.2 Ecotoxicity/environmental risk assessment

The applicant has not provided a full environmental risk assessment (ERA) in accordance with the guideline (CHMP/SWP/4447/00). Instead, justification for the absence of a full ERA is supplied. Since Amikacin 125ml/250 ml solution for injection is a generic product, it will not lead to an increased exposure to the environment. Further environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of amikacin are well known. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As amikacin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amikacin sulfate is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Briklin marketed by MAH.

This is a generic application; therefore, additional clinical studies are not required as bioequivalence has been established. Furthermore, as this is parenteral administration (administered intramuscularly and/or intravenously) for which pharmaceutical equivalence with the reference product has been demonstrated, bioequivalence studies are not required in accordance with the EMA guideline on the investigation of bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

The submitted clinical efficacy and safety overviews are based on the reference product data and on recent clinical data available in literature which further corroborate the positive risk-benefit balance of droperidol intended for intravenous use.

IV.2 Pharmacokinetics

In healthy adults, the mean serum half-life slightly exceeds 2 hours with an average total apparent distribution volume of 24 liters, approximately 28% of body weight. Serum plasma protein binding ranges from 0 to 11%. The average serum clearance rate is approximately 100 ml / min and the renal clearance rate is 94 ml / min in individuals with normal renal function.
Amikacin is eliminated by glomerular filtration as the predominant elimination pathway. Patients with impaired renal function or decreased glomerular filtration excrete the antibiotic much more slowly, extending the serum half-life. Therefore, renal function should be closely monitored and the dosage adjusted accordingly (see 4.2 Posology and method of administration, Renal impairment).
Following administration of the recommended dose, therapeutic levels of amikacin are found in bones, heart, gallbladder, and lung tissue along with significant concentrations in urine, bile, sputum, bronchial secretions, interstitial, pleural, and synovial fluid.
Data from multiple daily dose trials show that cerebrospinal fluid levels in normal infants are approximately 10 to 20% of serum concentrations and can reach 50% in meningeal inflammation.

Amikacin after intramuscular administration is rapidly absorbed and is well tolerated locally. In healthy adult volunteers, mean maximum serum concentrations of approximately 12, 16, and 21 mcg / ml are obtained one hour after single intramuscular doses of 250 mg (3.7 mg/kg), 375 mg (5 mg/kg), and 500 mg, (7.5 mg/kg), respectively. At 10 hours, plasma levels are approximately 0.3 mcg/ml, 1.2 mcg/ml and 2.1 mcg/ml, respectively. When the drug is administered at the recommended dose, there is no evidence of accumulation with repeated doses for 10 days.
In patients with normal renal function, 91.9% of an intramuscular dose is excreted unchanged in the urine within the first 8 hours and 98.2% within 24 hours. Mean urine concentrations for 6 hours are 563 mcg/ml after 250 mg, 697 mcg/ml after 375 mg and 832 mcg/ml after 500 mg.

Single doses of 500 mg (7.5 mg/kg) that were administered to healthy adult volunteers with a 30-minute infusion gave mean maximal serum concentrations of 38 mcg/ml at the end of infusion and concentrations of 24 mcg/ml, 18 mcg/ml and 0,75 mcg/ml at 30 minutes, 1 hour and 10 hours after infusion, respectively. 84% of the administered dose was excreted in the urine in 9 hours and 94% in 24 hours. Repeated injections of 7.5 mg/kg every 12 hours in normal adults were well tolerated and did not result in drug accumulation.
Intravenous administration of single doses of 15 mg/kg over 30 minutes in adult volunteers with normal renal function resulted in mean peak serum concentrations of 77 mcg/ml and levels of 47 mcg/ml and 1 mcg/ml in 1 and 12 hours, respectively, after injection. Mean serum concentrations of 55 mcg/ml are observed after infusion of 15 mg/kg over 30 minutes in elderly patients (mean creatinine clearance 64 ml/min) with serum concentrations of 5.4 mcg/ml in 12 hours and 1.3 mcg/ml in 24 hours after

infusion. In multiple dose studies, no accumulation effects have been shown in patients with normal renal function who have received single daily doses of 15 to 20 mg/kg.

In a single study of newborns (1-6 days of after birth) grouped by birth weight (<2000, 2000-3000 and >3000g) amikacin was administered intramuscularly and/or intravenously at a dose of 7.5 mg/kg. Clearance in neonates >3000 g was 0.84 ml/min/kg and terminal half-life was about 7 hours. In this group, the initial volume of distribution and volume of distribution at steady state was 0.3 ml/kg and 0.5 ml/kg, respectively. In the lower birth weight groups the clearance/kg was lower and the half-life longer. Repeated dosing every 12 hours in all the specified groups showed no accumulation after 5 days.

IV.3 Pharmacodynamics

Amikacin acts via the inhibition of protein synthesis at the bacterial ribosome through interaction with the ribosomal RNS and subsequent inhibition of the translation in susceptible microbes. This results in a bactericidal action.

IV.4 Clinical Efficacy

The clinical efficacy of this combination of amikacin is well established. No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application.

IV.5 Clinical Safety

The clinical safety of this combination of amikacin is well established. No additional safety clinical studies to demonstrate safety have been included in the application.

A risk management plan was submitted, 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 Amikacin 125mg/ml, 250mg/ml, Solution for injection/infusion. Routine pharmacovigilance and routine risk minimisation activities are considered appropriate. The submitted Risk Management Plan is considered acceptable.

Periodic Safety Update Reports (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.

IV.6 Discussion on the clinical aspects

This is a generic application, the application dossier has been submitted in accordance with the Directive 2001/83/EC, as amended as a generic 10(1) application.

The reference product is well established in the EU being authorised since 1974. Amikacin sulfate has demonstrated efficacy and has a well-established documented safety profile.

This is a generic application, therefore additional clinical studies are not required as bioequivalence has been established. Furthermore, as this is parenteral administration (administered intramuscularly and/or intravenously) for which pharmaceutical equivalence with the reference product has been demonstrated, bioequivalence studies are not required in accordance with the EMA guideline on the investigation of bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

The product information is in line with that of the reference product.

V. OVERALL CONCLUSIONS

Amikacin 125 mg/ml and 250 mg/ml solution for injection/infusion are generic forms of Briklin (MAH: Vianex AE) authorised in Greece since 1974. Briklin is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Amikacin 125 mg/ml and 250 mg/ml solution for injection/infusion demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New DCP as RMS	IE/H/1239/001-002/DC	SmPC, PIL, IPAR	24th May 2024	23rd May 2029