IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Amikacin Caragen 250 mg/ml solution for injection/infusion
Amikacin
PA22939/001/001

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.

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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 Caragen Limited on 25th June 2021 for *the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including Pseudomonas species, Escherichia coli, indole-positive and indole-negative Proteus species, Providencia sp, Klebsiella sp, Enterobacter sp, Serratia sp and Acinetobacter sp. Amikacin may also be indicated for the treatment of known or suspected staphylococcal disease. The principal Gram-positive organism sensitive to amikacin is Staphylococcus aureus, including some methicillin-resistant strains. Amikacin has some activity against other Gram-positive organisms including certain strains of Streptococcus pyogenes, Enterococci and Diplococcus pneumoniae.*

This assessment and approval was under the national procedure.

The legal basis was Article 10(1), a generic procedure, using a suitable reference medicinal product: Briklin Solution for Injection 500mg/2ml marketed by Vianex S.A.

The legal status for the marketing authorisation is subject to medical prescription, which may not be renewed.

The Summary of Product Characteristics (SmPC) and Patient information leaflet for this medicinal product is available on the HPRA's website.

Name of the product	Amikacin Caragen 250 mg/ml solution for injection/infusion
Name(s) of the active substance(s) (INN)	Amikacin
Pharmacotherapeutic classification (ATC code)	J01GB06 amikacin
Pharmaceutical form and strength(s)	Solution for injection/infusion; 250 mg/ml
Marketing Authorisation Number(s) in Ireland (PA)	PA22939/001/001
Marketing Authorisation Holder	Caragen Limited
MRP/DCP No.	N/A

II. QUALITY ASPECTS

II.1. Introduction

This application is for Amikacin Caragen 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 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. or are adequately controlled by the manufacturer's specifications.

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.7 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. requirements.

P.8 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 and Pharmaceutical 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 Caragen 250 mg/ml solution for injection/infusion.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Briklin Solution for Injection 500 mg/2 ml on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Amikacin Caragen 250 mg/ml solution for injection is a generic product, it will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

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

Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the national procedure is comparable with that accepted for the reference product Briklin Solution for Injection 500mg/2ml marketed by Vianex S.A, and is also comparable with SmPCs for similar products from other procedures.

In a generic application the applicant does not have to provide new clinical trial data, and instead can bridge to the data used for the approval of a suitable reference medicinal product. For this generic application, the applicant has also not submitted any bioequivalence or comparative bioavailability studies as this is an aqueous parenteral product containing the same active substance and comparable excipients to that of the reference product.

IV.2 Pharmacokinetics

Amikacin is rapidly absorbed after intramuscular injection. Peak plasma concentrations equivalent to about 20 mg/ml are achieved one hour after IM doses of 500 mg, reducing to about 2 µg/ml 10 hours after injections.

Twenty per cent or less is bound to serum protein and serum concentrations remain in the bactericidal range for sensitive organisms for 10 to 12 hours.

Single doses of 500 mg administered as an intravenous infusion over a period of 30 minutes produce a mean peak serum concentration of 38 µg/ml. Repeated infusions do not produce drug accumulation in adults with normal renal function. However, decreased renal function will lead to accumulation.

In adults with normal renal function the plasma elimination half-life of amikacin is usually 2-3 hours. 94 - 98% of a single IM or IV dose of amikacin is excreted unchanged by glomerular filtration within 24 hours. Urine concentrations of amikacin average 563 µg/ml in the first 6 hours following a single 250 mg IM dose and 163 µg/ml over 6-12 hours. Following a single 500 mg IM dose urine concentrations average 832 µg/ml in adults with normal renal function.

Amikacin diffuses readily through extracellular fluids and is excreted in the urine unchanged, primarily by glomerular filtration. It has been found in pleural fluid, amniotic fluid and in the peritoneal cavity following parenteral administration.

Data from multiple daily dose trials show that spinal fluid levels in normal infants are approximately 10 to 20% of the serum concentrations and may reach 50% in meningitis.

In neonates and particularly in premature babies, the renal elimination of amikacin is reduced. In a single study in newborns (1-6 days of postnatal age) grouped according to birth weights (<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 mg/kg, respectively. In the groups with lower birth weight clearance/kg was lower and half-life longer. Repeated dosing every 12 hours in all the above groups did not demonstrate accumulation after 5 days.

IV.3 Pharmacodynamics

Amikacin is a semi-synthetic aminoglycoside antibiotic derived from Kanamycin A. It is active against a broad spectrum of Gram-negative organisms, including pseudomonas, Escherichia coli and some Gram-positive organisms, e.g. Staphylococcus aureus.

Aminoglycoside antibiotics are bactericidal in action. Although the exact mechanism of action has not been fully elucidated, the drugs appear to inhibit protein synthesis in susceptible bacteria by irreversibly binding to 30S ribosomal subunits.

IV.4 Clinical Efficacy

No new clinical studies were completed which is acceptable for an abridged/generic application.

IV.5 Clinical Safety

No new clinical studies were completed which is acceptable for an abridged/generic application.

Risk Management Plan

The risk management plan proposed by the applicant, including the proposed pharmacovigilance activities and risk minimisation measures is considered acceptable. The approved summary of safety concerns is outlined in the table below:

Important identified risks	• Hypersensitivity and anaphylaxis • Renal toxicity • Ototoxicity • Neuromuscular toxicity
Important potential risks	• Macular infarction following intravitreous administration (off label use) of amikacin • Increased exposure of amikacin in neonates on concomitant use with indomethacin • Medication error • Overgrowth of non-susceptible organisms • Safety during pregnancy
Missing information	• Use during lactation • Safety of amikacin longer than 14 days

Routine risk minimisation measures and routine pharmacovigilance activities are proposed to address the safety concerns outlined above and this is considered acceptable.

The Applicant should submit Periodic Safety Update Reports (PSUR) Periodic Safety Update Reports (PSUR) 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

Amikacin Caragen 250 mg/ml solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of a suitable approved reference product. Amikacin Caragen 250 mg/ml solution for injection/infusion is a well-known medicinal product with an established favourable efficacy and safety profile. No clinical studies or bioequivalence/bioavailability studies are considered necessary.

V. OVERALL CONCLUSIONS

Amikacin Caragen 250 mg/ml solution for injection/infusion is a generic form of Briklin Solution for Injection 500/2 mg/ml marketed by Vianex S.A which is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

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 Caragen 250 mg/ml solution for injection/infusion has a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE