Public Assessment Report

Decentralised Procedure

Amikacin 250 mg/ml Solution for Injection/Infusion

(amine)

PRODUCT LICENCE NUMBER:
PL 11311/0604
EUROPEAN PROCEDURE NUMBER:
UK/H/6923/001/DC

Tillomed Laboratories Limited.
LAY SUMMARY

Amikacin 250 mg/ml Solution for Injection/Infusion
(amikacin)

This is a summary of the Public Assessment Report (PAR) for Amikacin 250 mg/ml Solution for Injection/Infusion. It explains how Amikacin 250 mg/ml Solution for Injection/Infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Amikacin 250 mg/ml Solution for Injection/Infusion.

For practical information about using Amikacin 250 mg/ml Solution for Injection/Infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Amikacin 250 mg/ml Solution for Injection/Infusion and what is it used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Biklin 500 mg/2 ml solution for injection.

Amikacin 250 mg/ml Solution for Injection/Infusion is an antibiotic used to treat serious infections in adults and children including, infants less than 4 weeks old.

Areas of application include infections of the respiratory tract and the lungs, the urinary and genital tract, the gastrointestinal tract, inflammation of the inner lining of the heart (endocarditis), infected burns as well as bacterial infections of the blood associated with one of the infections mentioned. Amikacin 250 mg/ml Solution for Injection/Infusion may also be used to treat patients with low white blood cell counts (neutropenia) who have fever due to bacterial infection.

How does Amikacin 250 mg/ml Solution for Injection/Infusion work?
Amikacin belongs to the class of medicines known as aminoglycoside antibiotics. It works by killing bacteria or preventing their growth.

How is Amikacin 250 mg/ml Solution for Injection/Infusion used?
The pharmaceutical form of this medicine is solution for injection/infusion and the route of administration is via an injection/infusion either into a muscle or vein two to three times daily. The dose of Amikacin 250 mg/ml Solution for Injection/Infusion will be adjusted by the patient’s doctor depending on the severity of their infection, the sensitivity of the pathogen, kidney function, age and their body weight.

The treatment duration is generally 7 to 10 days.

For further information on how Amikacin 250 mg/ml Solution for Injection/Infusion is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription. The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.
What benefits of Amikacin 250 mg/ml Solution for Injection/Infusion have been shown in studies?
Amikacin 250 mg/ml Solution for Injection/Infusion is a generic medicine that fulfils criteria meaning that no additional studies are required. Amikacin 250 mg/ml Solution for Injection/Infusion has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics. Further information is provided in the main body of the PAR.

What are the possible side effects of Amikacin 250 mg/ml Solution for Injection/Infusion?
Because Amikacin 250 mg/ml Solution for Injection/Infusion is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Amikacin 250 mg/ml Solution for Injection/Infusion approved?
It was concluded that, in accordance with EU requirements, Amikacin 250 mg/ml Solution for Injection/Infusion has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Amikacin 250 mg/ml Solution for Injection/Infusion?
A Risk Management Plan (RMP) has been developed to ensure that Amikacin 250 mg/ml Solution for Injection/Infusion is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Amikacin 250 mg/ml Solution for Injection/Infusion
A Marketing Authorisation was granted in the UK on 22 March 2019.

The full PAR for Amikacin 250 mg/ml Solution for Injection/Infusion follows this summary.

This summary was last updated in April 2019.
# TABLE OF CONTENTS

Contents

I  INTRODUCTION ...........................................................................................................5
II QUALITY ASPECTS .......................................................................................................7
III NON-CLINICAL ASPECTS ........................................................................................9
IV CLINICAL ASPECTS ..................................................................................................9
V USER CONSULTATION ...............................................................................................10
VI Overall conclusion, benefit/risk assessment and recommendation .....................10
Table of content of the PAR update .............................................................................17
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Amikacin 250 mg/ml Solution for Injection/Infusion (PL 11311/0604; UK/H/6923/001/DC) could be approved.

The product is indicated in the treatment of following infections in adults and pediatric patients including neonates (see section 5.1 of the SmPC)
- Hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP)
- Complicated Urogenital tract infections including pyelonephritis
- Complicated Intraabdominal infections
- Endocarditis (only in combination with other antibiotics),
- Infected burns

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Amikacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The Reference Member State (RMS) for this procedure was the UK and the Concerned Member State (CMS) was Sweden.

Amikacin is a kanamycin-derived semisynthetic aminoglycoside antibiotic. The mechanism of action of amikacin is due to a disruption of protein biosynthesis on the bacterial ribosome by interaction with the rRNA and subsequent inhibition of translation. This results in a bactericidal effect.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine. The reference medicinal product is Biklin 500 mg/ 2 ml solution for injection, which was first granted in the EU to Bristol-Myers Squibb, Austria on 02 August 1978. Amikin Injection 500 mg/ 2 ml is the equivalent reference product in the UK (PL 00125/0092R).

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

A biowaiver was submitted with this application, which was accepted. No bioequivalence study was required and no new clinical studies were provided with this application.

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this/these application(s) and are satisfactory.
The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 21 February 2019. After a subsequent national phase, a licence was granted in the UK on 22 March 2019.
II QUALITY ASPECTS

II.1 Introduction
Each ml of clear, colourless to light straw-coloured solution for injection/infusion contains 250 mg of amikacin (as sulphate).
Each 2 ml vial contains 500 mg of amikacin (as sulphate).
Each 4 ml vial contains 1 g of amikacin (as sulphate).

In addition to the active substance amikacin, this product also contains the excipients sodium metabisulfite (E223), sodium citrate dihydrate, sulfuric acid and water for injection.

Amikacin 500mg/2ml (250mg/ml) is packaged in a 2ml clear Type-I glass vial with a dark grey, chlorobutyl rubber stopper and a flip off seal and is available in pack sizes of 1 and 5 vials.

Amikacin 1g/4ml (250mg/ml) is packaged in a 5ml clear Type-I glass vial with a dark grey, chlorobutyl rubber stopper and a flip off seal and is available in pack sizes of 1 and 5 vials. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE(S)

rINN: Amikacin sulfate

Chemical Name: 6-O- (3-Amino-3-deoxy-α-D-glucopyranosyl)-4-O-(6-amino-6-deoxy-α-D-glucopyranosyl)-1-N-[(2S)-4-amino-2-hydroxybutanoyl]-2-deoxy-α-D-streptamine sulfate

Molecular Formula: C_{22}H_{47}N_{5}O_{21}S_{2}

Chemical Structure:

Molecular Weight: 782 g/mol
Appearance: White or almost white powder
Solubility: The substance is freely soluble in water, Practically insoluble in acetone and in 96% ethanol.

Amikacin sulfate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied.
Satisfactory specifications 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 for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. 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 complies with the current European regulations concerning materials in contact with food.

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

II.3 DRUG PRODUCT(S)

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

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 and has shown satisfactory results.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years with no special storage conditions is acceptable.

This product is intended for single use. Residual quantities are to be discarded.
After dilution:
Chemical and physical in use stability has been demonstrated for 36 hours at 25°C, 30 days at -15°C and 60 days at 4°C.
From a microbiological point of view, the 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°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of amikacin are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of amikacin is well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV.2 Pharmacokinetics
No new pharmacokinetic data have been submitted for this application and none were required.
IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety
No new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Biklin 500 mg/2 ml solution for injection.

IV.6 Risk Management Plan (RMP)
The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amikacin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product(s).

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.
TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

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<th>Product information affected</th>
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