Public Assessment Report

Decentralised Procedure

Tobramycin 40 mg/ml Solution for Injection or Infusion

Procedure No: UK/H/5097/002/DC

UK Licence No: PL 28176/0104

Strides Arcolab International Limited
LAY SUMMARY

Tobramycin 40mg/ml Solution for Injection or Infusion
(tobramycin, solution for injection or infusion, 40 mg/ml)

This is a summary of the public assessment report (PAR) for Tobramycin 40mg/ml Solution for Injection or Infusion (PL 28176/0104; UK/H/5097/002/DC). It explains how Tobramycin 40mg/ml Solution for Injection or 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 Tobramycin 40mg/ml Solution for Injection or Infusion.

For practical information about using Tobramycin 40mg/ml Solution for Injection or Infusion, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as Tobramycin Solution for Injection or Infusion in this report.

What is Tobramycin Solution for Injection or Infusion and what is it used for?
Tobramycin Solution for Injection or Infusion is a ‘generic’ medicine. This means that Tobramycin Solution for Injection or Infusion is similar to a reference medicine already authorised in the European Union (EU) called Nebcina Injection 40mg/ml (Eurocept International B.V., Denmark).

Tobramycin Solution for Injection or Infusion contains the active substance tobramycin (as tobramycin sulphate). Tobramycin Solution for Injection or Infusion is an antibiotic medicine that can be used to treat infections of the:
- brain;
- stomach and intestines;
- bladder or kidney (urinary tract infections);
- lungs (lower respiratory tract infections);
- skin and soft tissue, including burns.

Tobramycin may also be considered in serious staphylococcal infections for which penicillin or other less potentially toxic medicines cannot be used.

How is Tobramycin Solution for Injection or Infusion used?
Tobramycin Solution for Injection or Infusion is administered in the muscle or into a vein by a health professional. A doctor will work out the correct dose of Tobramycin to be administered, depending on the seriousness of the infection being treated as well as the patient’s medical condition, size, age and kidney function.

For further information on how Tobramycin Solution for Injection or Infusion is used, please see the Summary of Product Characteristics available on the MHRA website.

Tobramycin Solution for Injection or Infusion can only be obtained on prescription.

How does Tobramycin Solution for Injection or Infusion work?
Tobramycin Solution for Injection or Infusion kills bacteria that cause infections.

How has Tobramycin Solution for Injection or Infusion been studied?
The company (Strides Arcolab International Limited) has provided data from the published literature on tobramycin.

No additional studies were needed as Tobramycin Solution for Injection or Infusion is a generic
medicine that is an aqueous solution that is given by injection and contains the same active substance as
the reference medicine, Nebcina Injection 40mg/ml (Eurocept International B.V., Denmark).

**What are the benefits and risks of Tobramycin Solution for Injection or Infusion?**
Because Tobramycin Solution for Injection or Infusion is considered to be a generic medicine and is
bioequivalent to the reference medicine, its benefits and risks are taken as being the same as those of the
reference medicine.

**Why is Tobramycin Solution for Injection or Infusion approved?**
It was concluded that, in accordance with EU requirements Tobramycin Solution for Injection or
Infusion has been shown to have comparable quality and is considered to be bioequivalent to Nebcina
Injection 40mg/ml (Eurocept International B.V., Denmark). Therefore, the view was that, as for Nebcina
Injection 40mg/ml (Eurocept International B.V., Denmark), the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Tobramycin Solution for
Injection or Infusion?**
Safety information has been included in the Summary of Product Characteristics and the package leaflet
for Tobramycin Solution for Injection or Infusion, including the appropriate precautions to be followed
by healthcare professionals and patients.

**Other information about Tobramycin Solution for Injection or Infusion.**
A Marketing Authorisation was granted in the UK on 28 April 2014.

The full PAR approved for Tobramycin 40mg/ml Solution for Injection or Infusion follows this
summary.

For more information about treatment with Tobramycin 40mg/ml Solution for Injection or Infusion, read
the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2014.
TABLE OF CONTENTS

Module 1: Information about the initial procedure ........................................... Page 5

Module 2: Summary of Product Characteristics ................................................ Page 6

Module 3: Patient Information Leaflet .............................................................. Page 7

Module 4: Labelling ........................................................................................... Page 8

Module 5: Scientific discussion during the initial procedure ................................ Page 10
   I Introduction
   II About the product
   III Scientific overview and discussion
   III 1 Quality aspects
   III 2 Non-clinical aspects
   III 3 Clinical aspects
   IV Overall conclusion and benefit/risk assessment

Module 6: Steps taken after the initial procedure ............................................. Page 16
# Module 1

## Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Tobramycin 40 mg/ml Solution for Injection or Infusion</th>
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</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
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<tr>
<td>Active Substance</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Form</td>
<td>Solution for injection or infusion</td>
</tr>
<tr>
<td>Strength</td>
<td>40 mg per vial</td>
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<tr>
<td>MA Holder</td>
<td>Strides Arcolab International Limited, Unit 4, Metro Centre, Tolpits Lane, Watford, Hertfordshire, WD 18 9SS, UK</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Germany, Finland and Norway</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/5097/002/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 12 March 2014</td>
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</table>
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Tobramycin 40 mg/ml Solution for Injection or Infusion

Each ml of solution for injection or infusion contains Tobramycin sulphate equivalent to 40 mg of Tobramycin.
Disodium edetate, Sodium bisulphite, Sulfuric Acid, Sodium hydroxide and water for injections.
Read the package leaflet before use.
Keep out of the sight and reach of children.
This medicinal product does not require any special storage conditions.
Please refer package leaflet for in-use storage conditions.
Discard any unused solution immediately after initial use.
Use as directed by the Physician.

PL 28176/0104

Details to be overprinted

Dimension: 90 x 35 x 50 mm (Approx size)
Tobramycin 40mg/ml Solution for Injection or Infusion

Intravenous injection/Infusion or Intramuscular injection.
Read the package leaflet before use.

Strides Arcolab International Ltd.
PL 28176/0104 POM

Batch EXP
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Tobramycin 40 mg/ml Solution for Injection or Infusion (PL 28176/0104; UK/H/5097/002/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated in the treatment of the following serious infections caused by susceptible micro-organisms:

- acute bacterial meningitis; peritonitis;
- complicated and recurrent urinary tract infections, including pyelonephritis and cystitis;
- nosocomial lower respiratory tract infections, including severe pneumonia;
- skin, soft tissues infections including burns.

Tobramycin injection may be considered in serious staphylococcal infections for which penicillin or other less potentially toxic drugs are contra-indicated and when bacterial susceptibility testing and clinical judgement indicate its use.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Germany, Finland and Norway as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Nebcina Injection, 40mg/ml (Eurocept International B.V., Denmark), which was granted in Denmark on 12 July 1974. The corresponding reference product in the UK is Nebcin Injection 40mg/ml (PL 13621/0059) which was granted to Flynn Pharma Limited on 12 September 2011 following several change of ownership procedures of the product originally granted to Eli Lilly and Company Limited on 08 March 1974.

The active ingredient, tobramycin (as tobramycin sulphate), is an aminoglycoside antibiotic. Tobramycin is bactericidal and acts by inhibiting protein synthesis in bacterial cells.

No new non-clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that have been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product, containing the same active substance as the reference product.

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.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 12 March 2014. After a subsequent national phase, a licence was granted in the UK on 28 April 2014.
### II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Tobramycin 40 mg/ml Solution for Injection or Infusion</th>
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<tbody>
<tr>
<td>Name of the active substance (INN)</td>
<td>Tobramycin</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antibacterials for systemic use, other aminoglycosides (ATC code: J01GB01)</td>
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<td>Pharmaceutical form and strength</td>
<td>Solution for injection or infusion; 40 mg/ml</td>
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<tr>
<td>Reference number for the Decentralised Procedure</td>
<td>UK/H/5097/002/DC</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>Germany, Finland and Norway</td>
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<tr>
<td>Marketing Authorisation Number</td>
<td>PL 28176/0104</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Strides Arcolab International Limited, Unit 4, Metro Centre, Tolpits Lane, Watford, Hertfordshire, WD 18 9SS, UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Tobramycin
Chemical name: 4-O-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-6-O-(2,6-diamino-2,3,6-trideoxy-α-D-ribo-hexopyranosyl)-L-streptamine.
Molecular formula: C_{18}H_{37}N_{5}O_{9}
Structure:

![Chemical Structure Image]

Mr: 467.51
Appearance: White or almost white powder.
Solubility: Freely soluble in water, very slightly soluble in ethanol (96 per cent).

Tobramycin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, tobramycin, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT

Other Ingredients
Other ingredients consist of the pharmaceutical excipients disodium edetate, sodium bisulfite (E222), sulfuric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of sodium bisulfite (E222), which complies with a suitable in-house specification. Certificates of Analysis have been provided for all excipients, showing compliance with their respective 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 safe, efficacious, stable solution for injection or infusion that was equivalent to the reference product Nebcina Injection, 40 mg/mL (Eurocept International B.V, Denmark).

Suitable pharmaceutical development data have been provided for this application.

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 that have shown satisfactory results.
Control of Finished Product
The finished product specification is acceptable. Test methods have been described that 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 Type I tubular flint moulded vials with bromo butyl dark grey rubber stoppers and flip off aluminium seals. The product is packaged with the Patient Information Leaflet in cardboard outer cartons, in a pack size of 10 vials x 2ml.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply 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 unopened product, with no special storage conditions. After opening or dilution, the product should be used immediately.

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

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this type of application for a parenteral product.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of tobramycin 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 the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

The grant of a Marketing Authorisation is recommended.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
The clinical pharmacology of tobramycin is well-known. 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 a parenteral product. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

Efficacy
No new efficacy data have been submitted and none are required for this type of application. The clinical efficacy of tobramycin is well-established.

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. The safety profile of tobramycin is well-known.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The PIL is consistent with the details in the SmPC and in line with current guidance. The labelling is in line with 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 Marketing Authorisation Holder (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.

Suitable justification has been provided for not submitting a Risk Management Plan for this application which was received prior to 21 July 2012, the date from which pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force. As the safety profile of the active substance is well-established, a Risk Minimisation Plan is not considered necessary. Routine Pharmacovigilance activities in accordance with EU regulations are considered sufficient.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Tobramycin 40 mg/ml Solution for Injection or 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 and none were required for this type of application. No bioequivalence studies were submitted or required for this application for a parenteral product.

SAFETY
The safety profile of tobramycin is well-known. No new or unexpected safety issues or 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. Tobramycin is a well-known active substance. Extensive clinical experience with tobramycin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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