COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tobramycine Steri-Neb 300 mg/5 ml, nebuliser solution (tobramycin)

NL/H/4711/001/DC

Date: 6 March 2023

This module reflects the scientific discussion for the approval of Tobramycine Steri-Neb 300 mg/5 ml, nebuliser solution. The procedure was finalised in the United Kingdom (UK/H/4346/01/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Public Assessment Report

Decentralised Procedure

Tymbrineb 300 mg/5 ml Nebuliser Solution

Procedure No: UK/H/4346/001/DC

UK Licence No: PL 00289/1437

Teva UK Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

Tymbrineb 300mg/5ml Nebuliser Solution (tobramycin)

This is a summary of the Public Assessment Report (PAR) for Tymbrineb 300 mg/5 ml Nebuliser Solution (PL 00289/1437; UK/H/4346/001/DC), formerly known as Tobramycin 300 mg/5 ml Nebuliser Solution. It explains how the application for Tymbrineb 300 mg/5 ml Nebuliser Solution was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Tymbrineb 300 mg/5 ml Nebuliser Solution.

For practical information about using Tymbrineb 300 mg/5 ml Nebuliser Solution, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as 'Tymbrineb Nebuliser Solution' in this report.

What is Tymbrineb Nebuliser Solution' and what is it used for?

Tymbrineb 300 Nebuliser Solution' is a 'hybrid generic medicine'. This means that Tymbrineb Nebuliser Solution' is similar to'reference medicines' already authorised in the UK containing the same active substance, but is available as a nebuliser solution.

The 'reference medicine' for Tymbrineb Nebuliser Solution' Nebcin Injection 40mg/ml (PL 14385/0004; King Pharmaceuticals Limited, COA 30/03/1998), which was originally granted a licence on 24 January 1991 to Eli Lilly and Company Limited and Tobi 300 mg/5ml Nebuliser Solution which was originally granted a licence on 10 December 1999 to Chiron Corporation Limited.

The Marketing Authorisation Holder (MAH; Teva UK Limited) has provided its own data to demonstrate the safety and efficacy of Tymbrineb Nebuliser Solution.The non-clinical/clinical data submitted in support of this application is abridged to the second reference product Tobi 300 mg/5ml Nebuliser Solution which was originally granted a licence on 10 December 1999 to Chiron Corporation Limited.

Tymbrineb Nebuliser Solution is used in patient s aged six years and older for treating chest infection in Cystic Fibrosis (CF) caused by a common bacterium, *Pseudomonas aeruginosa.*

Pursuant to the Orphan regulations, Teva UK Limited has obtained consent to market this product in the relevant Member States in the European Union.

How does Tymbrineb Nebuliser Solution work?

Tymbrineb Nebuliser Solution contains the active substance tobramycin, which is an aminoglycoside antibiotic. Tobramycin kills the bacterium Pseudomonas aeruginosa and so helps improves breathing. As tobramycin is inhaled, rather than taken as a pill, more of the antibiotic gets into the lungs.

How is Tymbrineb Nebuliser Solution used?

Tymbrineb Nebuliser Solution is for inhalation use, through the mouth.

This medicine should always be used exactly as instructed by the patient's doctor or pharmacist. The patient should check with the doctor or pharmacist if you are not sure.

The recommended dose is two ampoules per day for 28 days. The usual dose is the same for all persons aged 6 years and older. The patient should inhale the contents of one ampoule in the morning and one in evening. There should be a 12-hour gap between doses.

The patient then has 28 days without taking the medicine before starting another 28-day treatment course again.

It is important that the patient keeps using the product twice each day during the 28 days of treatment and keeps to the 28-day on/28-day off cycle.

Tymbrineb Nebuliser Solution should be used with a clean, dry PARI LC PLUS reusable nebuliser and a suitable compressor. The patient should ask his/her doctor or physiotherpist for advice on which compressor to use. The patient's doctor or physiotherapist can also advise on the proper use of the medicine and the equipment required. The patient may need different nebulisers for other inhaled medicines such as dornase alfa, which can be used to improve sputum clearance in CF.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Tymbrineb Nebuliser Solution can only be obtained with a prescription.

What benefits of Tymbrineb Nebuliser Solution have been shown in studies?

The MAH has provided data from the published literature on tobramycin showing the benefits of nebulised tobramycin.

What are the possible side effects of Tymbrineb Nebuliser Solution?

Like all medicines, Tymbrineb Nebuliser Solution can cause side effects although not everybody gets them.

For the full list of all side effects reported with Tymbrineb Nebuliser Solution, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Tymbrineb Nebuliser Solution.

Why is Tymbrineb Nebuliser Solution approved?

It was concluded that, in accordance with EU requirements, Tymbrineb Nebuliser Solution has been shown to have comparable quality and to be comparable to Nebcin Injection 40mg/ml. Therefore, the MHRA decided that, as for Nebcin Injection 40mg/ml, the benefits outweigh the identified risks and recommended that Tymbrineb Nebuliser Solution can be approved for use.

What measures are being taken to ensure the safe and effective use of Tymbrineb Nebuliser Solution?

Safety information has been included in the Summary of Product Characteristics and the package leaflets for Tymbrineb Nebuliser Solution, 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/reviewed continuously.

Other information about Tymbrineb Nebuliser Solution

Bulgaria, Czech Republic, Germany, Denmark, Ireland, Italy, the Netherlands, Portugal, Spain and the UK agreed to grant a Marketing Authorisation for Tobramycin 300 mg/5ml Nebuliser Solution on 03 November 2011. A Marketing Authorisation was granted in the UK on 22 December 2011. Subsequent to a variation procedure, the name of the product was changed to Tymbrineb 300 mg/5ml Nebuliser Solution.

The full PAR for Tymbrineb Nebuliser Solution and follows this summary.

For more information about treatment with Tymbrineb Nebuliser Solution read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2015.

SCIENTIFIC DISCUSSION

Tymbrineb 300mg/5ml Nebuliser Solution (tobramycin)

TABLE OF CONTENTS

Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Tobramycin 300 mg/5 ml Nebuliser Solution (PL 00289/1437; UK/H/4346/001/DC), could be approved. This application was submitted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Bulgaria, Czech Republic, Germany, Denmark, Ireland, Italy, the Netherlands, Portugal and Spain as Concerned Member States (CMS).

The product is a prescription-only medicine (POM) indicated for the long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients aged six years and older with cystic fibrosis (CF).

This application is made via the Decentralised Procedure (DCP), according to Article 10.3 of 2001/83/EC, as amended, as a hybrid application. In line with advice from the Co-ordination Group for Mutual Recognition and Decentralised Procedure – Human (CMD(h)) and current European guidelines the reference medicinal product for the purposes of data exclusivity for this application is Nebcin Injection 40mg/ml which was originally granted a licence on 24 January 1991 to Eli Lilly and Company Limited. The non-clinical/clinical data submitted in support of this application is abridged to a second reference product Tobi 300 mg/5ml Nebuliser Solution which was originally granted a licence on 10 December 1999 to Chiron Corporation Limited.

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It's mechanism of action is primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

No new non-clinical studies or clinical efficacy studies were conducted, which is acceptable given that this is a hybrid application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application.

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

The RMS and CMS considered that the application could be approved with the end of procedure (Day 209) on 03 November 2011. After a subsequent national phase, a licence wa granted in the UK on 22 December 2011.

Following approval of a variation application on 06 June 2013, the name of the product was changed to Tymbrineb 300 mg/5 ml Nebuliser Solution.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a clear to slightly yellow solution.

One single-dose 5 ml ampoule contains tobramycin 300 mg.

The product also contains the pharmaceutical excipients sodium chloride, water for injections, sulphuric acid (for pH-adjustment) and sodium hydroxide (for pH-adjustment). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is packaged in 5 ml single-dose low density polyethylene ampoules. Four ampoules are packed and sealed in a foil pouch. Each carton comprises of 14 (56 ampoules), 28 (112 ampoules) or 42 (168 ampoules) foil pouches.

It has been stated that not all pack sizes may be marketed, however, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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.

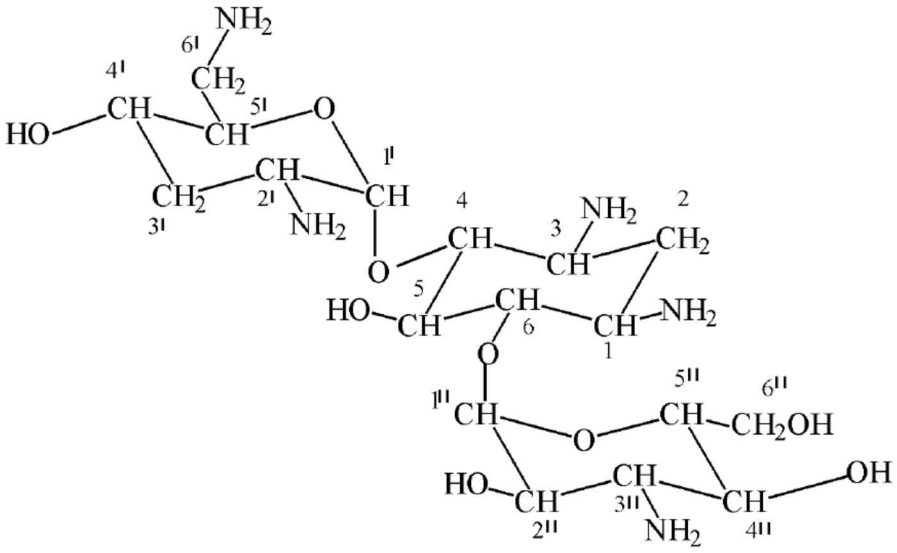
II.2 DRUG SUBSTANCE

Tobramycin

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.

Structure:



Molecular formula: $C_{18}H_{37}N_5O_9$

Molecular mass: 467.52

Appearance: Tobramycin is a white to off white hygroscopic powder. It is freely soluble in water, very slightly soluble in ethanol and practically insoluble in chloroform and ether.

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 (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the programme was to develop a stable nebuliser solution containing 300 mg/5 ml tobramycin as the active substance that is comparable in performance to the reference product Tobi 300 mg/5ml Nebuliser Solution.

A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity profiles have been provided for the proposed and originator products.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

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 at pilot scale and has shown satisfactory results. In addition the applicant has provided confirmation that commercial batch sizes will be validated in accordance with the requirements as defined in Annex 1 ‘Note for Guidance on Process Validation’ (CPMP/QWP/848/96, March 2001).

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System

The finished product is packaged in 5 ml single-dose low density polyethylene ampoules. Four ampoules are packed and sealed in a foil pouch. Each carton comprises of 14 (56 ampoules), 28 (112 ampoules) or 42 (168 ampoules) foil pouches.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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.

Stability of the product

Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘The foil pouches (intact or opened) may be stored at up to 25^{o}C for up to 28 days. Store in a refrigerator (2-8^{o}C). Do not freeze. Store in the original package to protect from light. The contents of the whole ampoule should be used immediately after opening’.

Bioequivalence/bioavailability
As the product provides local therapeutic activity (that is, not systemic), investigation of bioequivalence is not appropriate for this product.

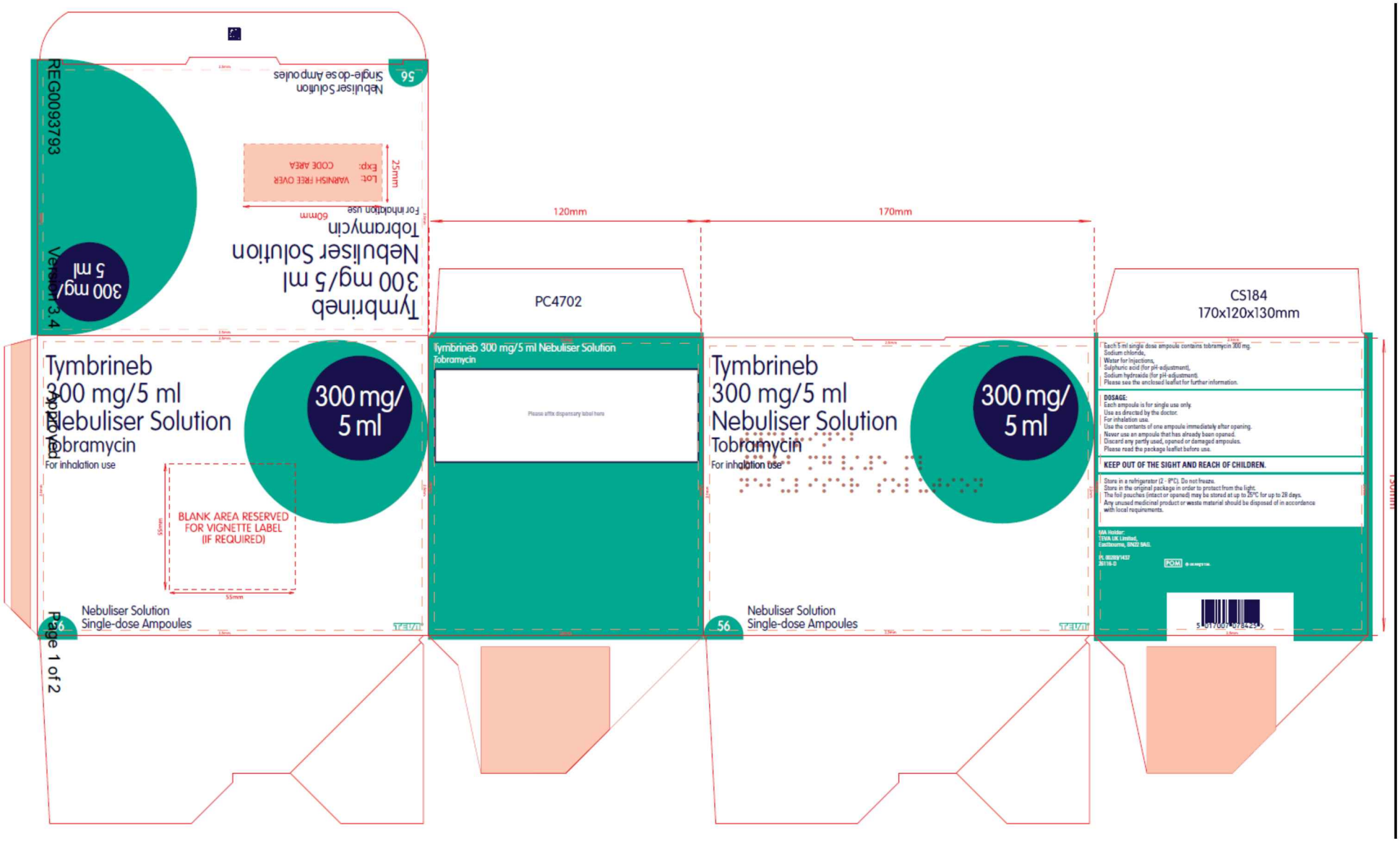
II.4 Discussion on chemical, pharmaceutical and biological aspects

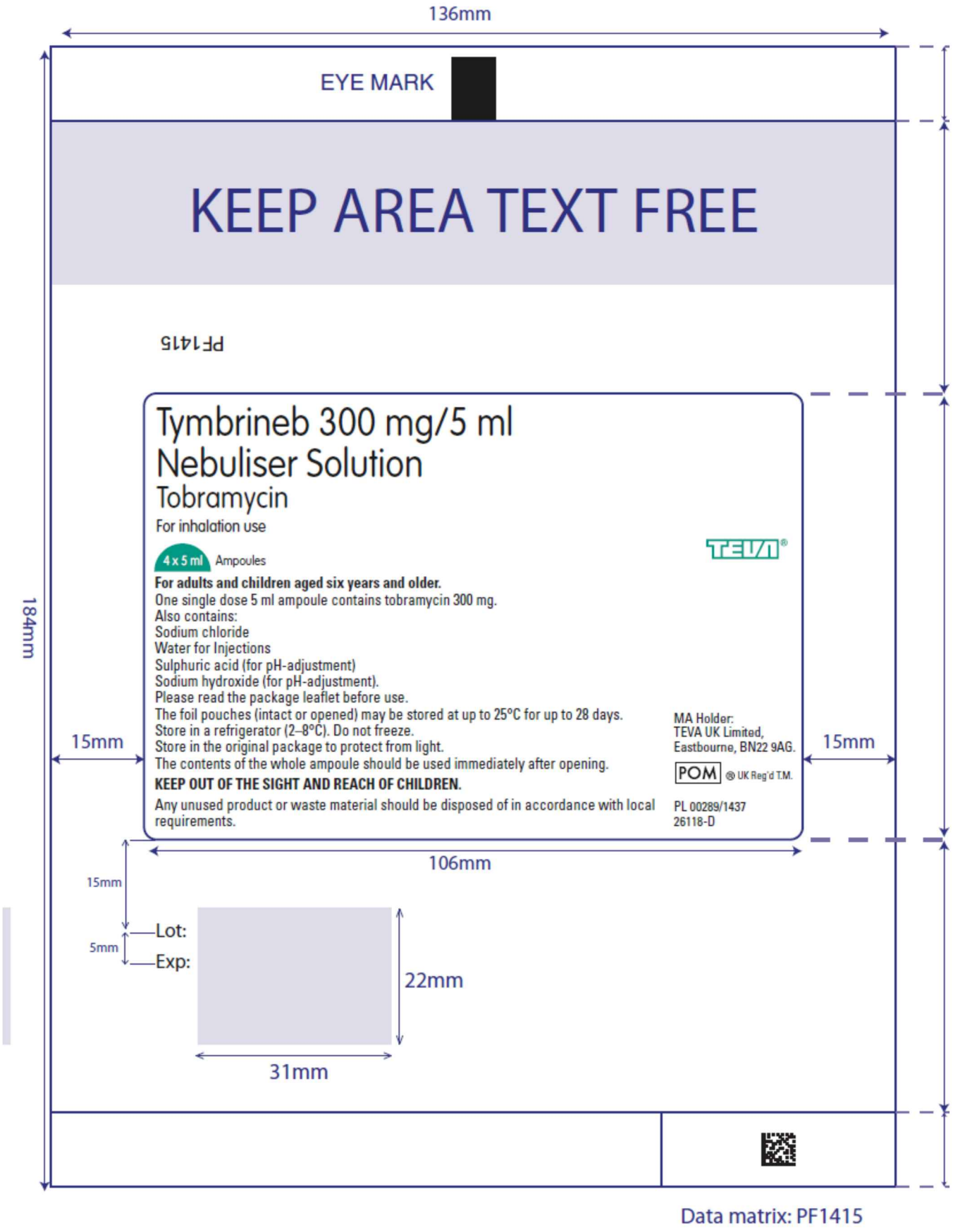
There are no objections to the approval of this product from a pharmaceutical viewpoint.

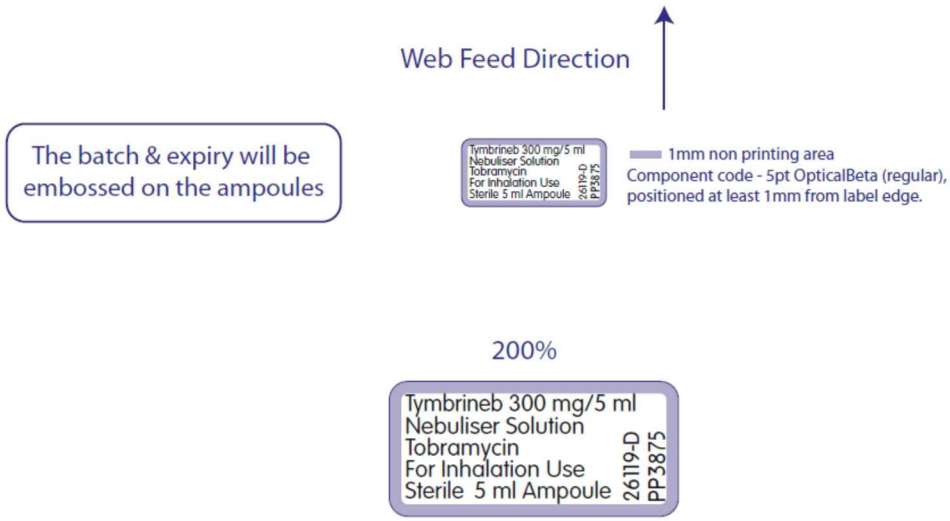
II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labels are acceptable.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs are available on the MHRA website. The current labelling is presented below:


REG0093793
Version 3.4
300 mg/ 5 ml
Tymbrineb 300 mg/5 ml Nebuliser Solution Tobramycin
For inhalation use
56 Single-dose Ampoules Nebuliser Solution
Lot: Exp: VARNISH FREE OVER CODE AREA
25mm
60mm
120mm
170mm
PC4702
Tymbrineb 300 mg/5 ml Nebuliser Solution
Tobramycin
Please affix dispensary label here
Tymbrineb 300 mg/5 ml Nebuliser Solution Tobramycin
For inhalation use
300 mg/ 5 ml
BLANK AREA RESERVED FOR VIGNETTE LABEL (IF REQUIRED)
55mm
55mm
Nebuliser Solution Single-dose Ampoules
56
Nebuliser Solution Single-dose Ampoules
56
CS184
170x120x130mm
Each 5 ml single dose ampoule contains tobramycin 300 mg.
Sodium chloride,
Water for injections,
Sulphuric acid (for pH-adjustment),
Sodium hydroxide (for pH-adjustment).
Please see the enclosed leaflet for further information.
DOSAGE:
Each ampoule is for single use only.
Use as directed by the doctor.
For inhalation use.
Use the contents of one ampoule immediately after opening.
Never use an ampoule that has already been opened.
Discard any partly used, opened or damaged ampoules.
Please read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Store in a refrigerator (2 - 8°C). Do not freeze.
Store in the original package in order to protect from the light.
The foil pouches (intact or opened) may be stored at up to 25°C for up to 28 days.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/1437
38116-0
POM
5 051007 018425
Approved
Page 1 of 2


136mm
EYE MARK
KEEP AREA TEXT FREE
PF1415
Tymbrineb 300 mg/5 ml
Nebuliser Solution
Tobramycin
For inhalation use
4 x 5 ml Ampoules
For adults and children aged six years and older.
One single dose 5 ml ampoule contains tobramycin 300 mg.
Also contains:
Sodium chloride
Water for Injections
Sulphuric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment).
Please read the package leaflet before use.
The foil pouches (intact or opened) may be stored at up to 25°C for up to 28 days.
Store in a refrigerator (2–8°C). Do not freeze.
Store in the original package to protect from light.
The contents of the whole ampoule should be used immediately after opening.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Any unused product or waste material should be disposed of in accordance with local requirements.
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
POM
® UK Reg'd T.M.
PL 00289/1437
26118-D
184mm
15mm
15mm
106mm
15mm
5mm
Lot:
Exp:
22mm
31mm
Data matrix: PF1415


Web Feed Direction
The batch & expiry will be embossed on the ampoules
Tymbrineb 300 mg/5 ml Nebuliser Solution Tobramycin For Inhalation Use Sterile 5 ml Ampoule 26119-D PP3875
1mm non printing area
Component code - 5pt OpticalBeta (regular), positioned at least 1mm from label edge.
200%
Tymbrineb 300 mg/5 ml Nebuliser Solution Tobramycin For Inhalation Use Sterile 5 ml Ampoule 26119-D PP3875

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of tobramycin are well known. No new non clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The 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.

III.2 Pharmacology

Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics

Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology

Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with other products already on the market it is not considered to increase the environmental risk. Thus, the applicant's justification is accepted.

III.6 Discussion of the non-clinical aspects

There are no objections to the approval of this product from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV.1 Introduction

Biowaiver

No clinical studies have been conducted to support the application. Essential similarity with the originator product is based on the comparative quality attributes of the product. This application is being made under Article 10.3 of Directive 2001/83/EC, which states that bioequivalence cannot be demonstrated through bioavailability studies for products for local use intended to act without systemic absorption. The proposed product, Tobramycin 300 mg/5 ml Nebuliser Solution, is a locally applied product (administered by inhalation). As suggested in the guidelines on the investigation of bioequivalence (EPMP/EWP/QWP/1401/98 Rev.1) and the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/293/95/95 Final), the conventional approach to determine bioequivalence based on systemic measurements is generally not applicable for products that are intended for local use only without systemic absorption.

The Applicant has not conducted any clinical studies with Tobramycin 300 mg/5 ml Nebuliser Solution. Tobramycin nebuliser solution is an aqueous solution. No bioequivalence studies are required for this type of product according to the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev1).

IV.2 Pharmacokinetics

No new data have been submitted and none are required.

IV.3 Pharmacodynamics No new pharmacodynamic data were submitted and none were required for this application.

IV.4 Clinical Efficacy

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of tobramycin is well-established from its extensive use in clinical practise.

IV.5 Clinical Safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan
A suitable justification has been provided for not submitting a Risk Management Plan for this product.

The Pharmacovigilance System, as described by the applicant, fulfils the requirements 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.

IV.7 Discussion of the clinical aspects There are no objections to the approval of this product from a clinical viewpoint.

V. USER CONSULTATION
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 leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Tobramycin 300 mg/5 ml Nebuliser Solution 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 an application of this type.

EFFICACY AND SAFETY
No clinical studies have been conducted to support the application. Essential similarity with the originator product is based on the comparative quality attributes of the product. This application is being made under Article 10.3 of Directive 2001/83/EC, which states that bioequivalence cannot be demonstrated through bioavailability studies for products for local use intended to act without systemic absorption. The proposed product, Tobramycin 300 mg/5 ml Nebuliser Solution, is a locally applied product (administered by inhalation). As suggested in the guidelines on the investigation of bioequivalence (EPMP/EWP/QWP/1401/98 Rev.1) and the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/293/95/95 Final), the conventional approach to determine bioequivalence based on systemic measurements is generally not applicable for products that are intended for local use only without systemic absorption.

The Applicant has not conducted any clinical studies with Tobramycin 300 mg/5 ml Nebuliser Solution. Tobramycin nebuliser solution is an aqueous solution. No bioequivalence studies are required for this type of product according to the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev1).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the originator product, where appropriate, and consistent with current guidelines.

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

Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

(Type II variations, PSURs, commitments)

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached
To change the medicinal product name in the UK from “Tobramycin 300 mg/5 ml Nebuliser Solution” to “Tymbrineb 300 mg/5ml Nebuliser Solution". As a consequence sections 1, 4.1, 4.2, 4.4, 4.6, 4.8, 4.9 & 6.5 of the UK Summary of Product Characteristics (SmPC) have been updated with the new name as well as the UK Labelling and Patient Information Leaflet (PIL) mock ups.	UK/H/4346/001/IB/004	SmPC, PIL and labelling	05/06/2013	06/06/2013	Approval	No
To update the SmPC and PIL, to bring the Paediatrics information in-line with the brand-leader (PL 00101/0935) after the publication of the Public Assessment Report for the Work-Sharing (WS) procedure FI/W/002/pdWS/001 on 23.08.2012. Also to update the SmPC, PIL and labelling documents in line with the most current QRD template.	UK/H/4346/001/IB/002	SmPC, PIL and labelling	22/07/2013	17/09/2013	Approval	No
To update sections 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, 6.2, 6.4 and 6.6 of the Summary of Product Characteristics (SmPC) in line with the reference product and in line with the QRD template. Consequently, the Patient Information Leaflet (PIL) and label has been updated.	UK/H/4346/001/IB/010	SmPC, PIL and labelling	20/05/2015	19/06/2015	Approval	Yes (Annex 1.1)

Annex 1.1

Our Reference:	PL 00289/1437, Application 17
Product:	Tymbrineb Nebuliser Solution 300 mg/5 ml
Marketing Authorisation Holder:	Teva UK Limited
Active Ingredient(s):	Tobramycin
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	UK/H/4346/001/IB/010

Reason:
To update sections 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, 6.2, 6.4 and 6.6 of the Summary of Product Characteristics (SmPC) in line with the reference product and in line with the Quality Review of Documents (QRD) template. Consequently, the Patient Information Leaflet (PIL) and label has been updated.

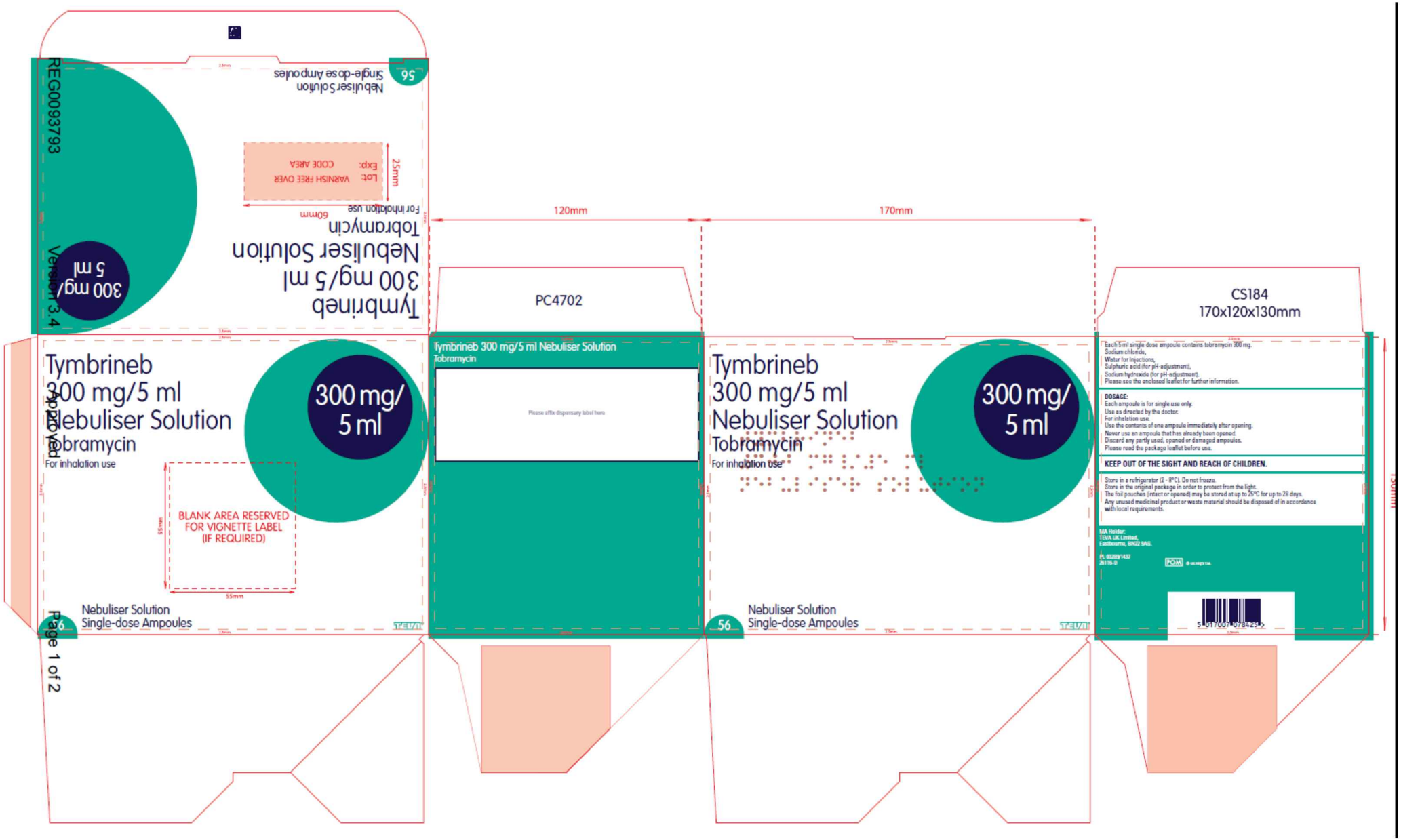
Linked / Related Variation(s) or Case(s):
Not applicable

Supporting Evidence
Revised SmPC fragments (sections), and updated labelling and leaflet have been provided
Evaluation
The updated sections of the SmPC and leaflet are acceptable. The updated labelling is acceptable.

Conclusion
The updated sections of the SmPC, the updated labelling and the leaflet are satisfactory and there are no objections to approval.

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

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs are available on the MHRA website. The current labelling is presented below:


REG0093793
Version 3.4
300 mg/5 ml
Tymbrineb
300 mg/5 ml
Nebuliser Solution
Tobramycin
For inhalation use
60mm
25mm
Lot: VARNISH FREE OVER
Exp: CODE AREA
Nebuliser Solution
Single-dose Ampoules
56
120mm
170mm
PC4702
CS184
170x120x130mm
Tymbrineb
300 mg/5 ml
Nebuliser Solution
Tobramycin
For inhalation use
300 mg/
5 ml
Approved
BLANK AREA RESERVED
FOR VIGNETTE LABEL
(IF REQUIRED)
55mm
55mm
Nebuliser Solution
Single-dose Ampoules
56
Tymbrineb 300 mg/5 ml Nebuliser Solution
Tobramycin
Please affix dispensary label here
Each 5 ml single dose ampoule contains tobramycin 300 mg.
Sodium chloride,
Water for injections,
Sulphuric acid (for pH adjustment),
Sodium hydroxide (for pH adjustment).
Please see the enclosed leaflet for further information.
DOSAGE:
Each ampoule is for single use only.
Use as directed by the doctor.
For inhalation use.
Use the contents of one ampoule immediately after opening.
Never use an ampoule that has already been opened.
Discard any partly used, opened or damaged ampoules.
Please read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Store in a refrigerator (2 - 8°C). Do not freeze.
Store in the original package in order to protect from the light.
The foil pouches (intact or opened) may be stored at up to 25°C for up to 28 days.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
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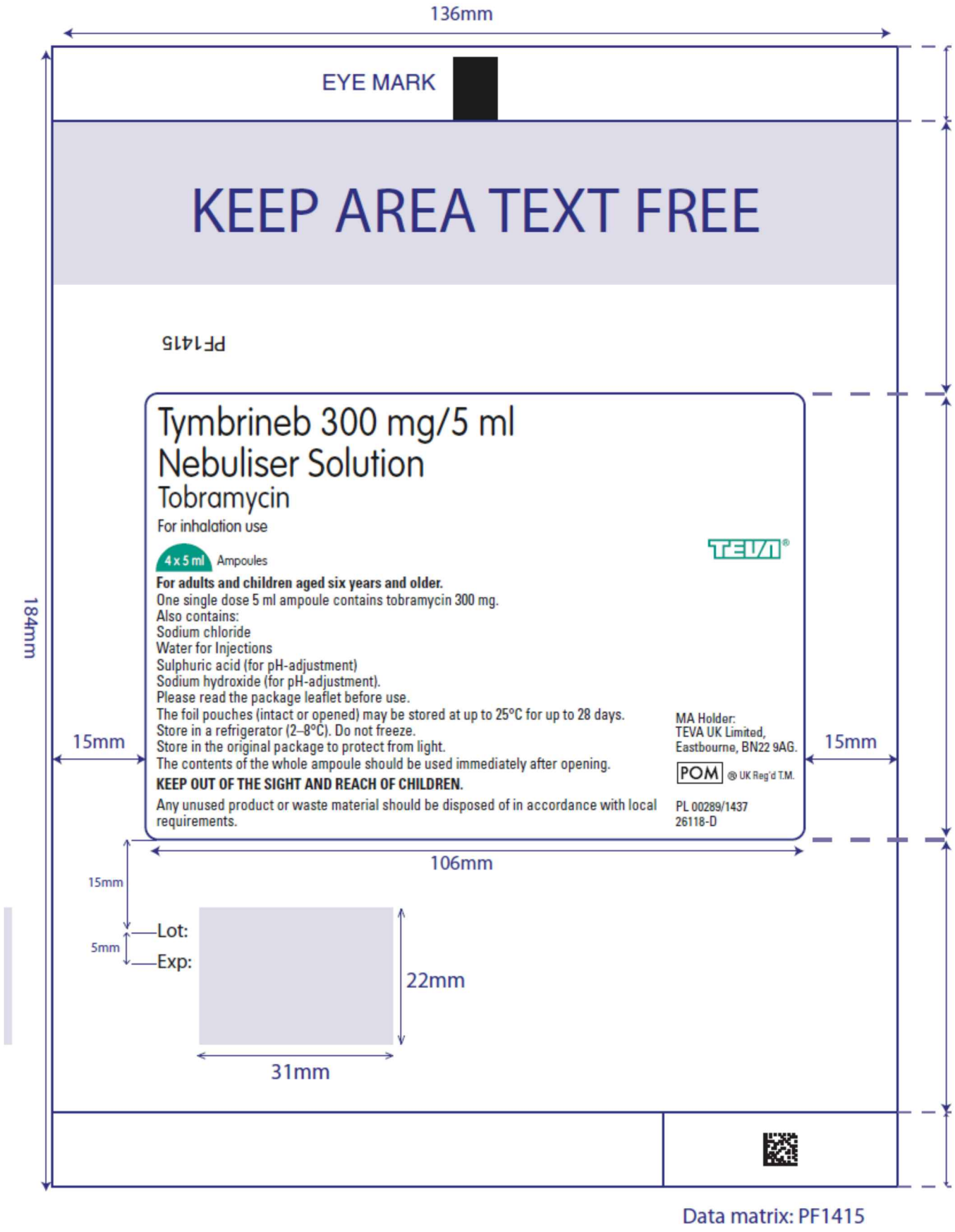
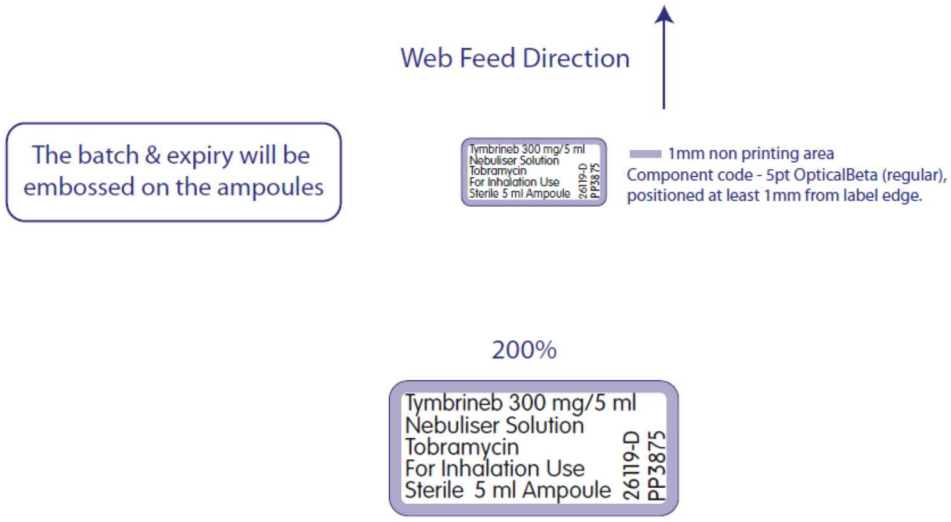
150mm

Page 1 of 2


136mm
EYE MARK
KEEP AREA TEXT FREE
PF1415
Tymbrineb 300 mg/5 ml
Nebuliser Solution
Tobramycin
For inhalation use
4 x 5 ml Ampoules
For adults and children aged six years and older.
One single dose 5 ml ampoule contains tobramycin 300 mg.
Also contains:
Sodium chloride
Water for Injections
Sulphuric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment).
Please read the package leaflet before use.
The foil pouches (intact or opened) may be stored at up to 25°C for up to 28 days.
Store in a refrigerator (2–8°C). Do not freeze.
Store in the original package to protect from light.
The contents of the whole ampoule should be used immediately after opening.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Any unused product or waste material should be disposed of in accordance with local requirements.
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
POM ® UK Reg'd T.M.
PL 00289/1437
26118-D
184mm
15mm
15mm
106mm
15mm
5mm
Lot:
Exp:
22mm
31mm
Data matrix: PF1415



Decision – Approved 22 June 2015.