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: 4 December 2025

This report reflects the scientific discussion for the approval of Tobramycine Steri-Neb 300 mg/5 ml, nebuliser solution. The procedure was finalised on 3 November 2011 in the United Kingdom (UK/H/4346/01/DC). After a transfer in 2018, the current RMS is the Netherlands. As a result, the product name, procedure number and layout have been updated in this report. For information on other changes after the finalisation date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CF	Cystic Fibrosis
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
POM	Prescription-Only Medicine (UK)
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Tobramycine Steri-Neb 300 mg/5 ml, nebuliser (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 40 mg/ml which was originally granted a licence on 9 March 1974 to Eli Lilly and Company Limited. The non-clinical/clinical data submitted in support of this application is abridged to a second product, Tobi 300 mg/5 ml 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*. Its 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 was granted in the UK on 22 December 2011.

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.

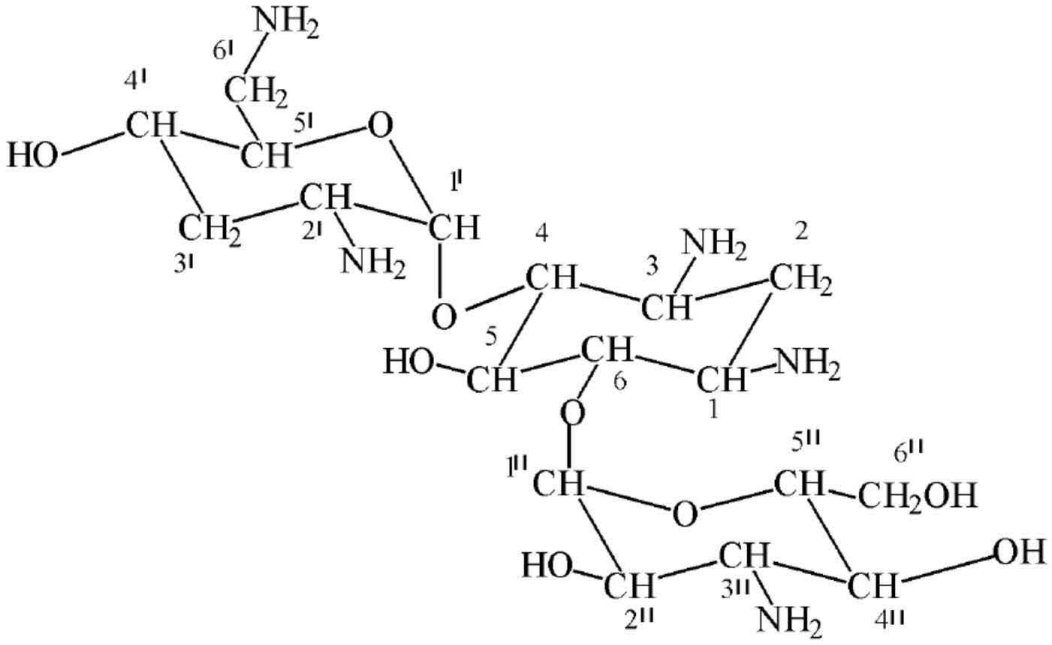
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

Tobramycin

INN:	Tobramycin
Chemical name:	4-O-(3-Amino-3-deoxy-a-D-glucopyranosyl)-2-deoxy-6-O-(2,6-diamino-2,3,6-trideoxy-a-D-ribo-hexopyranosyl)-L-streptamine.

Structure:



Molecular formula:	C18H37N5Og
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.

Manufacturing process

All aspects of the manufacture are covered by a European Directorate for the Quality of medicines (EDQM) Certificate of Suitability.

Quality control of drug substance

All aspects of the control of the active substance tobramycin are covered by a European Directorate for the Quality of medicines (EDQM) Certificate of Suitability.

Stability of drug substance

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 Nebcin Injection 40 mg/ml.

A satisfactory account of the pharmaceutical development has been provided.

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

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

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).

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.

Control of excipients

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

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 .

Quality control of drug product

The important quality characteristics of Tobramycine Steri-Neb 300 mg/5 ml, nebuliser solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch.

Stability of drug 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°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'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the excipients are of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

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 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.3 Discussion on 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, Tobramycine Steri-

Neb 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 Tobramycine Steri-Neb 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, pharmacodynamics and clinical efficacy and safety

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 practice.

IV.3 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.4 Discussion on the clinical aspects

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

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

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.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approved/ non Approved	Summary/ Justification for refuse
UK/H/4346/ 001/IA/001	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	No	17-01-2013	Approved	N.A.
UK/H/4346/ 001/1B/002	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC - Implementation of wording agreed by the competent authority 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 AR for the 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	Yes: SmPC, PIL and labelling	17-09-2013	Approved	N.A.

UK/H/4346/001/IA/003	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Secondary packaging site	No	30-05-2013	Approved	N.A.
UK/H/4346/001/1B/004	Change in the (invented) name of the medicinal product - for Nationally Authorised products To change the medicinal product name in the UK from "Tobramycin 300 mg/5 ml labelling 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.	SmPC, PIL and labelling	06-06-2013	Approved	N.A.
UK/H/4346/001/IB/005	Change in the (invented) name of the medicinal product - for Nationally Authorised products To change of name of the medicinal product from, Tobramycine 300mg/5ml PCH verneveloplossing, to Tobramycine Steri-Neb 300mg/5 ml verneveloplossing in the Netherlands only. There are no updates to the UK product information.	Yes	20-09-2013	Approved	N.A.
UK/H/4346/001/IA/006	Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	No	13-03-2014	Rejected	
UK/H/4346/001/IA/007	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place	No	25-03-2014	Approved	N.A.
UK/H/4346/001/IB/008	Change to in-process tests or limits applied during the	No	7-05-2014	Approved	N.A.

	manufacture of the finished product - Other variation				
UK/H/4346/001/IB/009	Change in the specification parameters and/or limits of the finished product - Other variation	No	4-12-2014	Approved	N.A.
UK/H/4346/001/1B/010	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH 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 SPC in line with the reference product and in line with the QRD template. Consequently, the PIL and label has been updated. See Annex 1.1	Yes: SmPC, PIL and labelling	19-06-2015	Approved	N.A.
UK/H/4346/IA/011/G	B.I.b).2. a) Minor changes to an approved test procedure B.II.d).2. a) Minor changes to an approved test procedure	No	16-06-2015	Approved	N.A.
UK/H/4346/001/IA/012	Change in the name and/or address of the marketing authorisation holder	No		Approved	N.A.
UK/H/4346/001/IB/013	Change in the (invented) name of the medicinal product - for Nationally Authorised products To change the name (de-brand) of the finished product from "Tymbrineb 300 mg/5 ml Nebuliser Solution" to "Tobramycin 300 mg/2 ml Nebuliser Solution" in the UK. Consequentially sections 1, 4.1, 4.2, 4.9 and 6.5 of the SPC, label and leaflet have been updated.	Yes: SmPC, PIL and labelling	19-11-2015	Approved	N.A.
UK/H/4346/001/IA/014	Change in the name and/or address of the marketing authorisation holder	No	22-04-2016	Approved	N.A.
UK/H/4346/IA/015/G	Change in name of the active substance or of an excipient	Yes	11-07-2016	Approved	N.A.

	Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method	No			
UK/H/4346/001/IA/016	Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits	No	20-01-2017	Approved	N.A.
UK/H/4346/001/IB/017	Change in the (invented) name of the medicinal product - for Nationally Authorised products To change the name of the medicinal product in the United Kingdom only. The proposed new name will be Tymbrineb 300 mg/5 ml Nebuliser Solution.	Yes	6-04-2017	Approved	N.A.
UK/H/4346/001/R/001	Renewal	No	14-06-2018	Approved	N.A.
UK/H/4346/001/IB/018	Change in the (invented) name of the medicinal product - for Nationally Authorised products To register a change in the (invented) name of the medicinal product for Ireland.	Yes	10-08-2017	Approved	N.A.
UK/H/4346/II/019/G	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance - Addition of a new specification parameter to the specification with its corresponding test method Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the	No No	15-02-2018	Approved	N.A.

	manufacturing process of the active substance - Change outside the approved specifications limits range for the active substance Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance - Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method as a result of a safety or quality issue	 No			
UK/H/4346/001/IB/020	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Other variation	No	2-05-2018	Approved	N.A.
UK/H/4346/001/IB/021	Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	No	8-08-2018	Approved	N.A.
UK/H/4346/IB/022/G	Change in the specification parameters and/or limits of the finished product - Tightening of specification limits Change in the specification parameters and/or limits of the finished product - Other variation Change in the shelf-life or storage conditions of the finished product - Extension of the shelf life of the finished product - As packaged for sale	No No Yes	19-10-2018	Approved	N.A.

	(supported by real time data) To extend the registered shelf-life of the drug product from 2 years (24 months) to 3 years (36 months). Consequently, SmPC 6-3 is updated.				
NL/H/4711/001/IA/023	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	Yes	12-4-2019	Approved	N.A.
NL/H/4711/001/IA/024	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place	No	4-12-2019	Approved	N.A.
NL/H/4711/001/IA/025	2x Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer.	No	18-3-2020	Approved	N.A.

NL/H/4711/001/IA/026	Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	No	3-4-2020	Approved	N.A.
NL/H/4711/001/IB/027	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH. .	Yes	24-2-2022	Approved	N.A.
NL/H/4711/001/II/028	Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority*	No	23-9-2022	Approved	N.A.
NL/H/4711/001/II/029	Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority*	No	23-9-2022	Approved	N.A.
NL/H/4711/IA/030/G	Change in test procedure for active substance - Minor changes to an approved test procedure Change in test procedure for the finished product - Minor changes to an approved test procedure Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial	No No No	2-8-2022	Approved	N.A.

	Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
NL/H/4711/001/II/031	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation	Yes	9-4-2023	Approved	N.A.
NL/H/4711/001/IA/032	Change in the name and/or address of the marketing authorisation holder	Yes	28-3-2023	Approved	N.A.
NL/H/4711/001/IB/034	Changes in the PI texts intended to implement the outcome of PSUSA; Implementation of wording agreed by the competent authority that required additional minor assessment Implementation of CMDh position on the PRAC PSUR Assessment Report for tobramycin (PSUSA/0009315/202406) published on March 2025.	Yes	29-8-2025	Approved	N.A.

ANNEX 1.1 SUBMISSION OF UPDATED SUMMARY OF PRODUCT CHARACTERISTICS IN LINE WITH THE REFERENCE PRODUCT (UK/H/4346/001IB/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.

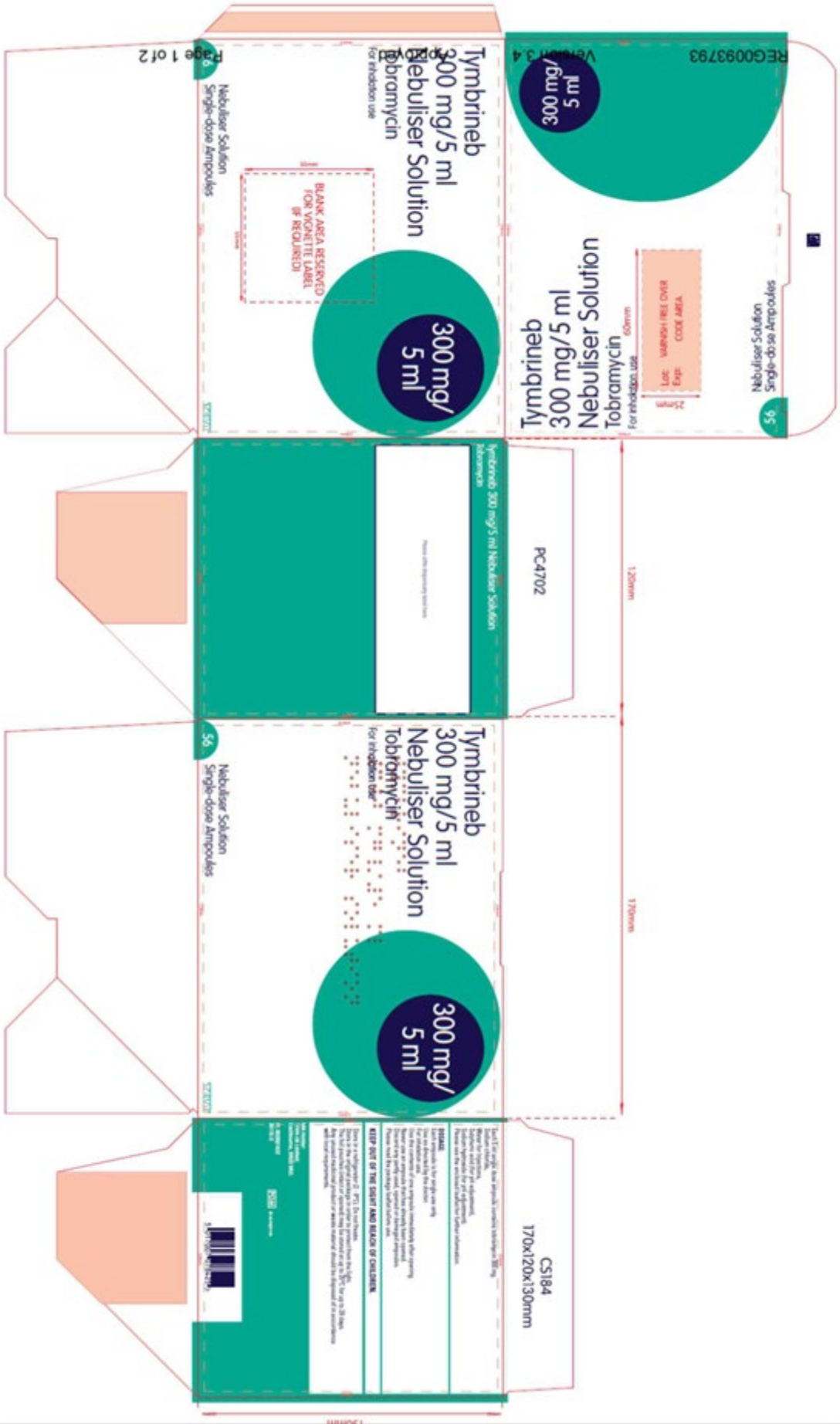
Linked/ Related Variation(s) or Case(s):
Not applicable

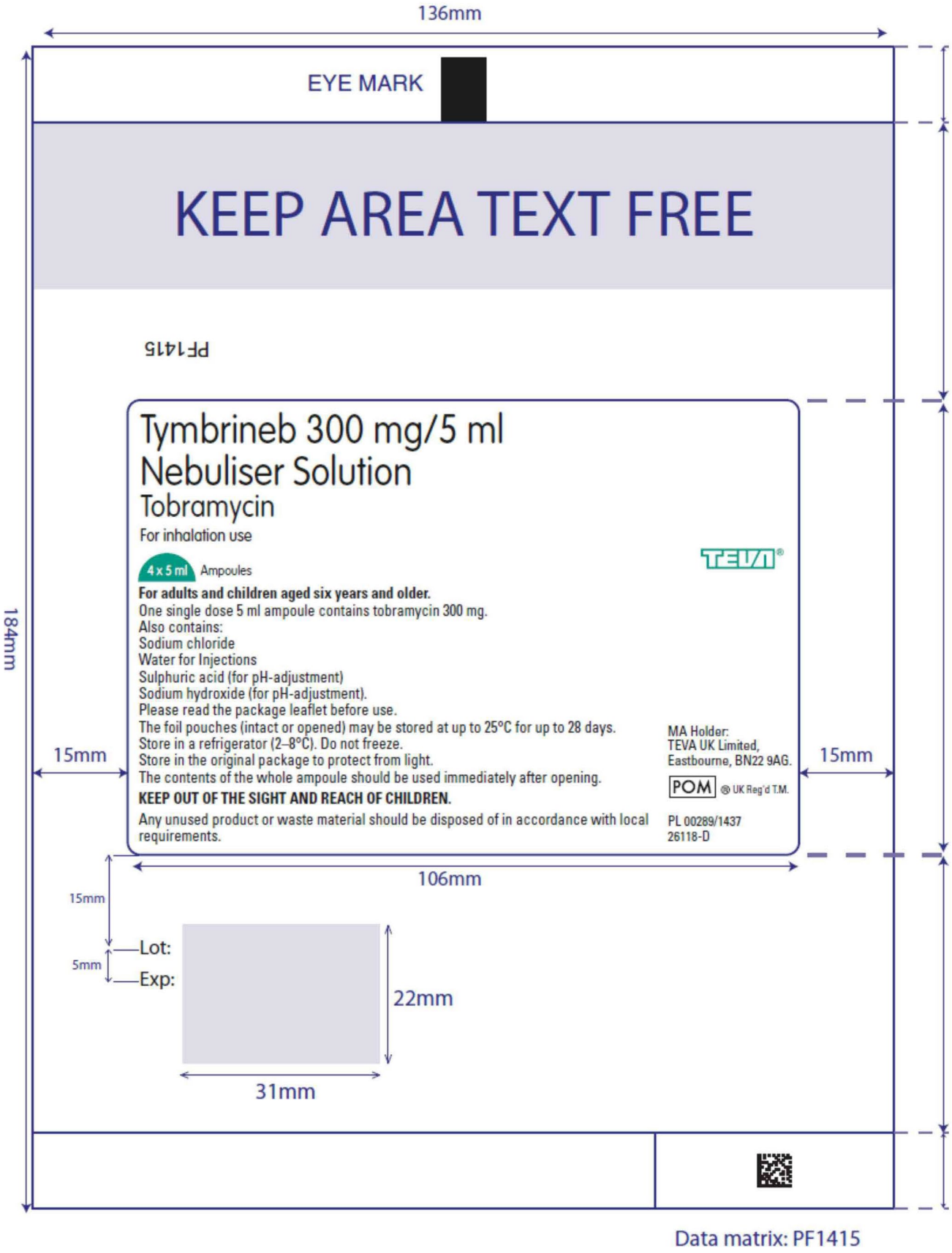
Supporting Evidence
Revised SmPC fragments (sections), and updated labelling and leaflet have been provided
Evaluation
The updated sections of the SmPC and leaflet are acceptable. The updated labelling is acceptable.

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 (Sm PCs) 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


Tymbrineb
300 mg/5 ml
Nebuliser Solution
Tobramycin
For inhalation use
300 mg/
5 ml
Nebuliser Solution
Single-dose Ampoules
56
BLANK AREA RESERVED FOR VIGNETTE LABEL IF REQUIRED
PC4702
120mm
170mm
CS184
170x120x130mm


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

200%

Tymbrineb 300 mg/5 ml
Nebuliser Solution
Tobramycin
For Inhalation Use
Sterile 5 ml Ampoule
26119-D
PP3875

Decision – Approved 22 June 2015.