CBG MEB

Public Assessment Report

Scientific discussion

Tobramycine SUN 300 mg/5 ml nebuliser solution

(tobramycin)

NL/H/3560/001/DC

Date: 3 May 2017

This module reflects the scientific discussion for the approval of Tobramycine SUN 300 mg/5 ml nebuliser solution. The procedure was finalised on 21 December 2016. For information on changes after this 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
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
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tobramycine SUN 300 mg/5 ml nebuliser solution from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients aged 6 years and older.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Tobramycin is an aminoglycoside antibiotic originally obtained from cultures of *Streptomyces tenebrarius*. It is used to treat various types of bacterial infections but is most active against aerobic Gram-negative rods.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming similarity with the innovator product TOBI 300 mg/5 ml nebuliser solution which was authorised in the UK in 1999. In the Netherlands Tobi 300 mg/5 ml nebuliser solution (NL License RVG 25484) has been registered by Novartis Pharma B.V. since 28 November 2000 through MRP UK/H/0361/001.

The concerned member states (CMS) involved in this procedure were Denmark, France, Germany, Hungary, Italy, Poland, Romania, Spain and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, as bioequivalence cannot be demonstrated through bioavailability studies.

Orphan status of Tobi Podhaler
A similar, orphan designated product, Tobi Podhaler (tobramycin inhaled as dry powder), has been approved in Europe since July 2011 via the centralised procedure (EU/1/10/652/001-003) for the indication 'suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis'.
Tobramycin SUN contains the same active ingredient (tobramycin), with the same mechanism of action and intended for a similar therapeutic indication as the orphan TOBI Podhaler product. A derogation is required to be able to grant the marketing authorisation. The holder of the marketing authorisation for the original orphan medicinal product has given his consent to Sun Pharmaceutical Industries Europe B.V. for the submission of this application.

II. QUALITY ASPECTS

II.1 Introduction

Tobramycine SUN 300 mg/5 ml is a clear, colourless to light yellow solution free from visible particulate matter with a pH between 4.5 to 6.5 and an osmolality between 135 to 285 mOsm/kg. The solution is packed in ready-to-use low density polyethylene ampoules with 5 ml of nebuliser solution containing tobramycin 300 mg as a single dose. The ampoules are packed in foil pouches.

The excipients are sodium chloride, water for injection, sulphuric acid (E513) (for pH adjustment), sodium hydroxide (E524) (for pH adjustment) and nitrogen (E941).

II.2 Drug Substance

The active substance is tobramycin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white powder, which is freely soluble in water, very slightly soluble in ethanol. Because he active substance is dissolved during the

manufacture of the drug product, the polymorphic state of the drug substance is not considered to be relevant.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
Tobramycin, non-sterile drug substance, is manufactured by a fermentation process from *Streptomyces tenebrarius*, followed by purification and recrystallisation steps. Assessment of the manufacturing process has been part of the CEP granting procedure.

Quality control of drug substance
The drug substance specification is almost identical to the CEP. The use of a different residual solvent method is acceptable. The specification is acceptable in view of the route of synthesis and various EU guidelines. Batch analytical data demonstrating compliance with the proposed drug substance specification have been provided for 3 batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies consisted of physicochemical and performance comparison of the proposed formulation with the reference product Tobi 300 mg/5 ml nebuliser solution. A range of pH values and effects of variation in temperature during shipping and handling were investigated. The compatibility and absorption of the filters, tubing and stainless steal were studied as well as the process holding times. A bioequivalence study is not required. The choice of manufacturing process and aseptic filtration as sterilisation method is justified. The choice of the packaging is justified by the results of the stability studies and a microbial challenge test. Drug product performance characteristics comparison was carried out, including mean nebulisation time, drug delivery rate by breath simulator, total drug substance delivered by breath simulator, aerodynamic assessment, fine particle dose, mass median aerodynamic diameter and geometric standard deviation.

Manufacturing process
The drug product is manufactured according to a standard process in five stages; preparation of a bulk solution by mixing and dissolution of all ingredients, followed by aseptic filtration, blow-fill-sealing of ampules, leak testing and visual inspection and packaging. The manufacturing process is adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 full scaled batches.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identity, absorbance and transmittance, pH, osmolality, uniformity of dosage units, particulate contamination, bacterial endotoxins, sterility, net content, related substances, sodium chloride content and assay. The release and shelf-life limits are identical and acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 full scaled batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the drug product has been provided for 3 full scaled batches stored at 2°C-8°C (18 or 30 months) and 25°C/40% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a LDPE ampoule which is further packed by a set of four in a sealed aluminum foil pouch. During the long term and accelerated stability studies all the tested parameters remain within the acceptance limits. The observed trends during the long term stability studies are similar to the accelerated study but less pronounced; a minimal increase of absorbance and a minimal decrease of transmittance. A photostability study is performed according to ICH Q1B conditions. It showed that the drug product is photolabile when directly exposed to light but photostable when stored in the LDPE ampule and as ampule in the sealed aluminium pouch. Based on the submitted 18 to 30 months stability data the proposed shelf-life of 2 years and storage conditions of "Store under refrigeration at 2°C - 8°C. Store in the original package in order to protect from light" can be granted. Based on the in-use stability data of three batches the claimed in-use stability of intact or opened pouches of up to 28 days at up to 25°C can be granted.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tobramycine SUN 300 mg/5 ml nebuliser solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tobramycine SUN is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of TOBI 300 mg/5 ml nebuliser solution which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tobramycin is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

To support comparability between the test Tobramycine SUN 300 mg/5 ml nebuliser solution and innovator Tobi 300 mg/5 ml nebuliser solution, *in-vitro* drug product performance characteristics comparison was carried out.

In vivo clinical studies can be waived in line with the Orally Inhaled Products (OIP) guideline (CPMP/EWP/4151/00 Rev. 1) because the proposed product satisfies the following criteria:

- the product contains the same active substance (tobramycin)
- the dosage form is identical (nebuliser solution)
- the active substance is in the liquid state (aqueous solution)
- no qualitative and/or quantitative differences in excipients are present (identical qualitative and quantitative composition)
- inhaled volume, handling of inhalation device and resistance to airflow for the test and reference products is similar (identical nebuliser - PARI LC PLUS - and inhalation instructions for method of administration in Sections 4.2 of both SmPCs)
- target delivered dose is similar, within ± 15%

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tobramycine SUN.

- Summary table of safety concerns as approved in RMP

Important identified risks	Cough Bronchospasm Haemoptysis
Important potential risks	Nephrotoxicity Ototoxicity Fetal harm Pathogen resistance: decreased P. Aeruginosa susceptibility to tobramycin Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxicity, neurotoxic and ototoxic drugs (class effects of parenteral use of aminoglycosides) Off-label use in children below 6 years of age
Missing information	Use in individuals after transplantation Use during pregnancy or lactation Use in population with disease severity different from clinical trial populations Use in population previously treated with aminoglycosides Use in patients with severe hepatic impairment Use in patients with moderate to severe renal failure Use in patients on diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides) generally not included in clinical trials Effects of medications prior to treatment (e.g. steroids, other antibiotics)

	Demographics of risk for aminoglycoside-related deafness in both Caucasians and Non-Caucasians

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. However, there is a theoretical possibility that Tobramycine SUN could be used (off label) with different nebulisers (e.g. eFlow rapid nebuliser system), especially when the use of other nebulisers reduces the treatment time. Currently it is not clear whether this would pose a safety risk.
Upon evaluation of spontaneous adverse event reports the MAH will take into account the nebuliser used and provide a thorough discussion in future PSURs.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tobi. No new clinical studies were conducted. Essential similarity is demonstrated based on comparative *in vitro* data only. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test was performed with 2 initial pilot tests and thereafter with 20 participants in 2 round. The questions covered the safety issues of the PL. 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

Tobramycine SUN 300 mg/5 ml nebuliser solution has a proven chemical-pharmaceutical quality and is a hybrid form of TOBI 300 mg/5 ml nebuliser solution. TOBI is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are solutions intended for inhalation use, no bioequivalence study is deemed necessary. Equivalence to the reference product was proven based on *in vitro* comparison.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tobramycine SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 December 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached