

Public Assessment Report

Scientific discussion

**Tobramycine Aristo 300 mg/5 ml, nebuliser
solution**

(tobramycin)

NL/H/4192/001/DC

Date: 9 April 2019

This module reflects the scientific discussion for the approval of Tobramycine Aristo 300 mg/5 ml, nebuliser solution. The procedure was finalised at 19 December 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CF	Cystic fibrosis
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tobramycine Aristo 300 mg/5 ml, nebuliser solution from Aristo Pharma GmbH.

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.

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

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

The concerned member states (CMS) involved in this procedure were Austria, Germany, Italy, and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

Orphan similarity

Tobramycine Aristo is similar to Tobi Podhaler (and not similar to Cayston). Argumentation is provided why a derogation of the market exclusivity for Tobramycine Aristo is granted with respect to the similarity of Tobi Podhaler (see IV. Clinical aspects).

II. QUALITY ASPECTS

II.1 Introduction

Tobramycine Aristo is a clear, slightly yellow nebuliser solution free from visible particles with pH 4.0-5.0 and osmolality 150-200 mOsm/kg.

The solution is packed in 5 ml single-use low density polyethylene ampoules. One ampoule contains 300 mg tobramycin. The content of one ampoule should be emptied into a nebuliser and administered by inhalation over approximately a 15-minute period. A hand-held PARI LC PLUS reusable nebuliser should be used with a suitable compressor (drug delivery rate 6.6 mg/min; total drug delivered 110.7 mg; mass median aerodynamic diameter (D50) 3.3; geometric standard deviation 2.3 µm; fine particle fraction 66.7%).

The excipients are sodium chloride, water for injections, sulphuric acid (E513), sodium hydroxide (E524).

II.2 Drug Substance

The active substance is tobramycin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Tobramycin is a white or almost white crystalline powder. The active substance is freely soluble in water, very slightly soluble in ethanol (96%). As the 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 Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for six batches; three from each possible manufacturing site.

Stability of drug substance

The active substance is stable for three 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The proposed product is an aqueous solution with an almost identical qualitative and quantitative composition as the reference product. A slight difference exists in the pH adjustment as the target pH for the proposed product differs slightly from that of the reference product. A waiver for clinical studies is proposed, and

therapeutic equivalence is demonstrated by comparative *in vitro* data for drug delivery rate, total dose delivered, volumetric mean diameter and geometric standard deviation.

Manufacturing process

The drug product is manufactured according to a non-standard process and consists of 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 has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for six batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Microbial attributes

Sterility control has been established following the requirements in the monograph of the United States Pharmacopoeia (USP) on tobramycin inhalation solutions and on the guideline on the pharmaceutical quality of inhalation and nasal products (EMA/CHMP/QWP/49313/2005).

Bacterial endotoxin control has been established following the requirements in the monograph of the USP on tobramycin inhalation solution, setting the limit established in this monograph.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, colour of solution, identity, uniformity of dosage units, extractable volume, pH, sodium chloride, assay, related substances, osmolality, sterility, bacterial endotoxins and particulate contamination. The release and shelf-life specification are almost identical, only a slightly wider limit for a specified impurity is proposed at shelf life. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on three batches of the proposed two batch sizes. The batches were stored at 2-8°C (12-36 months) and 25°C/60% RH (6 months). In addition, the batches were subjected to study potential water loss at 25°C/40% RH and 40°C/25% RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. All the parameters studied remain within specifications and no remarkable variation is observed along the study during long term and accelerated stability testing. Photostability studies were performed in

accordance with ICH recommendations and showed that the product is stable when exposed to light. It was further shown that freezing for 12 hours does not affect product quality. The proposed shelf-life of 36 months when stored in a refrigerator (2-8°C) is considered acceptable. No other storage recommendations are required. In use stability studies were conducted at 25°C/60% RH for 28 days. The data demonstrates that after removal from the refrigerator, or if refrigeration is unavailable, the product (intact or opened) remains stable up to 28 days when stored at up to 25°C.

Specific measures concerning 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 Aristo 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 Aristo 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

Similarity assessment

Where a designated orphan medicinal product has been authorised for the condition which covers the proposed therapeutic indication applied for, and a period of market exclusivity is in force, possible similarity should be discussed with the authorised orphan medicinal products.

Cayston (EU/3/04/204)

Tobramycin Aristo 300 mg/5 ml nebuliser solution and Cayston are intended for the same therapeutic indication. However Tobramycine Aristo neither contains a similar active substance as Cayston, nor has a similar structural formula nor has the same mechanism of action. Tobramycine Aristo is therefore not similar to Cayston.

Tobi Podhaler (EU/3/03/140)

It is demonstrated that Tobramycin Aristo is comparable to Tobi Podhaler. Both products have comparable parameters (molecular structural, mechanism of action, therapeutic indication).

Market exclusivity

Tobramycine Aristo is similar, within the meaning of Article 3 of Commission Regulation (EC) No 847/2000, to an authorised orphan medicinal product for the same therapeutic indication. The MAH therefore showed clinical superiority in order to receive a derogation of the market exclusivity as per Article 8(3) of Regulation (EC) No 141/2000.

Clinical superiority

The MAH substantiated a justification based on the EAGER study and its post hoc analyses with reference to publications of Konstan (2011) and Geller (2014). The EAGER study involves CF patients aged 6 years and above with chronic *Pseudomonas aeruginosa* lung infection. Tobi Podhaler (TIP) versus Tobi nebuliser solution (TIS) was compared in this trial. Safety was the primary endpoint of this study; nevertheless it was powered for efficacy (secondary endpoint) and therefore demonstrated non-inferiority in terms of efficacy only.

From the publications (Konstan, 2011; Geller, 2014) it is concluded that there is relevant difference in incidence of discontinuations and adverse events, in favour of the tobramycin nebuliser solution (TIS). The difference in discontinuation rate due to AEs was 13% after TIP

and 8% after TIS. The difference in incidence of adverse events is mainly driven by the difference in incidence of cough (cough occurred in 48.4% after TIP and 31.1% after TIS, cough suspected to be related to the study drug occurred in 25.3% after TIP and 4.3% after TIS, while at baseline cough was present in the same proportion of patients in both groups (42%)).

Furthermore the MAH argued that cough is a common side effect of TIP (experienced by at least 10% of the population), and when patients are experiencing cough, a nebuliser solution is the preferred product. The MAH’s assumption that for at least these 10% of the population tobramycin nebuliser solution provides a more favourable safety effect and provides an alternative treatment can be accepted. It is agreed that at least 10% of the target population to the orphan-designated medicinal product is considered substantial.

Conclusion

Based on the EAGER study data it is demonstrated that Tobramycine Aristo is clinical superior to Tobi Podhaler in the patient population experiencing cough. Clinical superiority is demonstrated based on safety. Adequate argumentation is provided why a derogation of the market exclusivity for Tobramycine Aristo can be granted with respect to the similarity of Tobi Podhaler.

Biowaiver

Tobramycine Aristo, as well as the reference product Tobi, is an aqueous solution intended for nebulization. The qualitative and quantitative composition in terms of active substance and excipients is the same for both products. In addition, both are administered using the same nebulizer device (PARI LC Plus nebulizer) and use compressors with the same technical characteristics (as stated in the SmPC). Therefore, following the directions stated in the Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00), it is not necessary to conduct studies directed to demonstrate the bioequivalence of both products. Results of *in vitro* comparison studies between the proposed medicinal product and Tobi nebuliser solution are provided. Based on these studies the product may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 Aristo.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> • Cough • Bronchospasm • Haemoptysis
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Important potential risks	<ul style="list-style-type: none"> • Nephrotoxicity • Ototoxicity • Foetal harm • Decreased Pseudomonas aeruginosa susceptibility to tobramycin (MIC) • Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides)
Missing information	<ul style="list-style-type: none"> • Patients with moderate or severe renal failure • Patients on diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs • Patients post organ transplantation • Pregnant or lactating females • Patients with disease severity different from that studied in clinical trials • Patients with co-morbidities (i.e. severe hepatic impairment) • Effects of medications prior to treatment (e.g. steroids, other antibiotics) • Demographics of risk for aminoglycoside-related deafness in both Caucasians and Non-Caucasians • Handling of the nebulizer in young paediatric patients (6-10 years)

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tobi 300 mg/5 ml nebuliser solution. No new clinical studies were conducted. The product is similar to the pharmacokinetic profile of the reference product. Furthermore the MAH demonstrated clinical superiority based on safety. 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 consisted of: a pilot test, followed by two rounds with ten participants each. The questions covered the

following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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 Aristo 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.

Therapeutic equivalence with Tobi 300 mg/5 ml nebuliser solution has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

A derogation of the market exclusivity for Tobramycine Aristo can be granted with respect to the similarity of Tobi Podhaler.

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 Aristo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 December 2018.

VII. REFERENCES

Konstan MW, Flume PA, Kappler M, Chiron R, Higgins M, Brockhaus F, Zhang J, Angyalosi G, He E, Geller DE. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *J Cyst Fibros.* 2011 Jan; 10(1):54-61.

Geller DE, Nasr SZ, Piggott S, He E, Angyalosi G, Higgins M (2014). Tobramycin inhalation powder in cystic fibrosis patients: response by age group. *Respir Care.* 59(3):388-98.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse