CBG MEB

Public Assessment Report

Scientific discussion

Zerseos 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution

(ipratropium bromide/salbutamol sulphate)

NL/H/3597/001/DC

Date: 6 June 2017

This module reflects the scientific discussion for the approval of Zerseos 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution. The procedure was finalised on 13 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 Zerseos 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution from Cipla (EU) Limited.

The product is indicated in the treatment of bronchospasm in patients older than twelve years of age with chronic obstructive pulmonary disease who require symptomatic treatment with both Ipratropium bromide and salbutamol.

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 Combivent UDVs, which has been marketed in the UK by Boehringer Ingelheim Limited since 1995. In the Netherlands, the reference product Combivent Unit Dose, nebuliser solution (NL License RVG 20233) has been registered by Boehringer Ingelheim B.V. since 1997 (original product).

The concerned member states (CMS) involved in this procedure were Germany, Spain, Ireland and Poland

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

In a number of member states the innovator product Combivent UDVs as registered in the UK is referred to as the European Reference Product.

II. QUALITY ASPECTS

II.1 Introduction

Zerseos 0.5 mg/2.5 mg per 2.5 ml is formulated as a clear, colourless solution with pH 3.80-4.80 and osmolality 278-349 mOsm/kg.

The nebuliser solution is packed in LDPE ampoules. Each 2.5ml ampoule contains 0.5 mg ipratropium bromide (as 525 micrograms ipratropium bromide monohydrate) and 2.5 mg salbutamol (as sulphate).

The excipients are sodium chloride, sulphuric acid (for pH adjustment) and water for injections.

II.2 Drug Substances

The active substances are ipratropium bromide monohydrate and salbutamol sulphate, established active substances described in the European Pharmacopoeia (Ph.Eur.). Ipratropium bromide is a white or almost white, crystalline powder, which is soluble in water, freely soluble in methanol and slightly soluble in alcohol. Salbutamol sulphate is a white or almost white, crystalline powder, which is freely soluble in water, slightly soluble in alcohol and in ether, and very slightly soluble in methylene chloride.
As the active substances are dissolved in the drug product, particle size and polymorphism are not critical.

The CEP procedure is used for both active substances. 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
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substances
The drug substances are tested in line with their Ph.Eur. monograph with additional tests on residual solvents as included on the CEP. Sufficient batch analysis data has been provided for both drug substances, demonstrating that the drug substances are of adequate quality.

Stability of drug substances
The CEP of ipratropium bromide states a retest period of 5 years if stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
For salbutamol sulphate stability data have been presented on full scaled batches. The results justify the claimed retest period of two years and no specific storage conditions are deemed necessary.

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 composition of the test and reference solutions is considered identical; the only minor difference is the very low amount of diluted sulphuric acid instead of diluted hydrochloric acid for pH adjustment. It is not expected that this minor difference affects the behaviour of the solution, the more because sulphate is also present in the test and reference product as salt of salbutamol. The difference in pH of the solution is acceptable in view of increased stability and in view of the pH ranges suitable for solutions for nebulisation. This difference in pH also does not affect the ionisation of the drug substances in view of their pKa values. No bioequivalence studies or clinical trials have been performed. As the proposed product is an aqueous solution for nebulisation with a practically identical composition as compared to the reference product, and the pH and osmolality of the drug product, the product is considered essentially similar to the reference product based on the in-vitro data. In view of that no clinical studies nor comparison of aerodynamic particle size distribution studies are required to support therapeutic equivalence.
Based on the pharmaceutical form and the identical composition of the proposed product compared to the reference product, the biowaiver is accepted in line with the applicable guideline for orally inhaled products.
The development of the manufacturing process and the choice of container closure system have been adequately discussed. The choice of aseptic processing and sterilisation by filtration is justified.
No overages of the active ingredients or excipients are required. In order to guarantee the nominal declared amount in the single-dose containers, a maximum overfill of 0.2 ml per container is applied.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by dissolution of sodium chloride in water, followed by the addition of ipratropium bromide and when dissolved, salbutamol sulphate is added and dissolved. The pH is then adjusted. The bulk solution is filtered and filled intro freshly formed LDPE ampoules. The filled and sealed ampoules are deflashed, leak tested and wrapped. The MAH validated the holding times of the bulk solutions before and after filtration. It concerns a non-standard (sterile) manufacturing process. The manufacturing process has been adequately validated for a maximum batch size.

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

Quality control of drug product
The drug product specification includes tests for description, identification (for both active substances and colour test for salbutamol), pH, fill volume (net content of respule), clarity of solution, colour, osmolality, uniformity of dosage units, water loss (only shelf-life), related substances, sterility, particulate contamination – sub-visible particles, assay for both drug substances, and packaging materials inspection.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on batches of two different sizes, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three production scaled batches stored at 25°C/60%RH (36 months) and 40°C/75%RH (6 months). Water loss testing was also performed under long-term (36 months at 25°C/40%RH) and accelerated (6 months at 40°C/20%RH) storage conditions. Results of two more recent production batches have been provided stored for 18 months at 25°C/40%RH and 6 months at 40°C/20%RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in LDPE FFS ampoules wrapped in a protective triple laminated polyester/aluminium/polythene pouch.

The photosensitivity of the drug product in the ampoules has been demonstrated. The light-protecting effect of the pouch and carton without pouch has been shown. With secondary packaging no significant changes were observed.

Under all storage conditions the impurity levels increase, however the results stay within the specifications. A decrease in pH and increase in water loss are observed as well. For the other parameters no specific trends or patterns were observed when stored under the proposed stability conditions. The proposed shelf-life of 24 months with the storage condition “do not store above 25°C; do not refrigerate or freeze”, which is in line with the reference product, is justified based on the stability data. The following is also stated: **“**Keep ampoules in the outer pouch or carton in order to protect from light”.

The results of the in-use study demonstrate stability of the ampoules for 3 months after opening of the pouch stored at 25°C/60%RH, provided that the ampoules are placed back in the pouch to protect from light.

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 for Zerseos 0.5 mg/2.5 mg per 2.5 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 for Zerseos 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 Combivent UDVs, 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

Ipratropium bromide and salbutamol sulphate are well-known active substances 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

The application does not include clinical demonstration of therapeutic equivalence versus Combivent UDVs nebuliser solution. According to the Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev. 1) the requirement for clinical studies may be waived when solutions for nebulisation have the same qualitative and quantitative composition as the reference product. This applies to the product at issue. As Zerseos is an aqueous solution for nebulisation with a practically identical composition as compared to the reference product, the product will also perform in the same way as the reference product. No nebuliser device is included neither in the package of Zerseos nor in that of the reference product. Based on the pharmaceutical form and the identical composition of the proposed product compared to the reference product, the biowaiver is accepted.

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 Zerseos 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution.

Summary of safety concerns as approved in RMP

Important identified risks	• Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) • Myocardial ischemia • Paradoxical bronchospasm • Anaphylactic reaction • Hypokalaemia • Narrow-angle glaucoma
Important potential risks	• Stroke • Off-label use in treatment of asthma in adolescents aged 12 to 17 years
missing information	• Safety in children less than 12 years of age • Use in pregnant and lactating women

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 Combivent UDVs nebuliser solution. No new clinical studies were conducted. The product is similar to this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet 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 with 4 participants, followed by two rounds with 10 participants each. The technical readability, comprehensibility of the text, traceability of information and the applicability were sufficiently investigated. 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

Zerseos 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution has a proven chemical-pharmaceutical quality and is a hybrid form of Combivent UDVs. Combivent is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are aqueous solutions intended for inhalation use, no bioequivalence study is deemed necessary. See SmPC and package leaflet for recommended nebulisers for use with Zerseos 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution.

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 Zerseos with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 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