Public Assessment Report

Scientific discussion

Budesonide Teva Steri-Neb 0.25 mg/2 ml, 0.5 mg/2 ml and 1 mg/2 ml, nebuliser suspension (budesonide)

NL/H/2714/001-003/DC

Date: 5 August 2014

This module reflects the scientific discussion for the approval of Budesonide Teva Steri-Neb nebuliser suspension. The procedure was finalised on 2 October 2013. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 9-11.

LIST OF ABBREVIATIONS

CQA	Critical Quality Attribute
EDTA	Ethylenediaminetetraacetic Acid
ERA	Environmental Risk Assessment
MAH	Marketing Authorisation Holder
OIP	Orally Inhaled Products
Ph.Eur.	European Pharmacopoeia
QbD	Quality by Design
QTPP	Quality Target Product Profile
SmPC	Summary of Product Characteristics
WHO	World Health Organization

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Budesonide Teva Steri-Neb 0.25 mg/2 ml, 0.5 mg/2 ml and 1 mg/2 ml, nebuliser suspension from Teva Nederland B.V.

The product is indicated for treatment of persistent bronchial asthma in patients where use of a pressurised inhaler or dry powder formulation is unsatisfactory or inappropriate.
A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application. The reference product is Pulmicort 250, 500 and 1000 Respules, containing 0.25 mg/0.5 mg/1 mg suspension for inhalation per 2 ml via a nebuliser (NL License RVG 15730, 14196-14197). These products have been registered in the Netherlands by AstraZeneca B.V. since 1992.

The concerned member states (CMS) involved in this procedure were Belgium, Cyprus, Germany, Denmark, Greece, Finland, Iceland, Ireland, Malta, Poland and Sweden. Post approval the marketing authorization was withdrawn in Germany.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, as equivalence to the innovator product cannot be demonstrated based on *in vivo* data. Bioequivalence based on systemic measurements of plasma concentration is generally not applicable for products that are intended for local use only without significant systemic absorption. In line with the applicable Guideline (EMEA/CHMP/QWP/49313/2005) a full range of *in vitro* tests was performed, including extensive *in vitro* comparative testing with the test product and the reference product Pulmicort Respules®.

II. QUALITY ASPECTS

II.1 Introduction

Budesonide Teva Steri-Neb is a white to off white suspension in a single dose ampoule. One ampoule of 2 ml suspension contains either 0.25 mg, 0.5 mg or 1 mg budesonide.
The single dose ampoule is made of low density polyethylene. Strips of five ampoule units are packed into a foil sachet and sachets are packed into a carton.

The excipients are: disodium edetate, sodium chloride, polysorbate 80 (E433), citric acid monohydrate (E330), sodium citrate (E331), water for injections

II.2 Drug Substance

The active substance is budesonide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white fine powder, which is practically insoluble in water, freely soluble in dichloromethane and sparingly soluble in ethanol.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>
The manufacturing process consists of two steps. Specifications on reagents, solvents and intermediate products have been provided. The information on the process is considered sufficient. The consistency of the polymorphic form has been adequately demonstrated.

Quality control of drug substance
The specification of the active substance is according to the Ph. Eur. specification for budesonide. The analytical procedures have been sufficiently described and validated. Batch analysis data have been presented for three batches, demonstrating compliance with the specification with consistent results.

Stability of drug substance
Long-term and accelerated stability studies have been performed with the micronised drug substance at 25°C/60% RH and at 40°C/75% RH, respectively. Long-term data cover a period of 60 months. Accelerated data were obtained for a period of 6 months. The proposed retest period of 5 years is justified by the stability data.

II.3 Medicinal Product

Pharmaceutical development
The development of the drug product has been described, the choice of excipients is justified and their functions explained. The choice of the sterilization process is regarded as justified.
The drug product was developed using a Quality by Design (QbD) approach. The proposed Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA) are considered appropriate. The QTPP is largely defined by the intended equivalence to the reference product Pulmicort Respules.
The MAH carried out an initial risk assessment on the potential effect of material attributes of the drug substance on the CQA of the drug product. The conclusion was that the potential effect of material attributes of the drug substance on the CQA of the drug product is low due to the control strategy or as a result of investigations. Risks identified as high are addressed by including EDTA in the formulation to reduce metal ions induced oxidation, to control the pH between 4 and 5 with a citric acid/sodium citrate buffer to reduce basic degradation, and to use a secondary packaging that protects from photolytic degradation. Due to the control strategy, the MAH identified the risks as being low.
The test product has been compared with the reference product by *in vitro* equivalence studies following the requirements of the Guideline on the pharmaceutical quality of inhalation and nasal products (NfG/CHMP/QWP/49313/2005Corr). The comparison included total delivered dose and dose delivery rate, aerodynamic assessment of particle size distribution, and droplet size distribution. The applied methods and statistical approach are acceptable and demonstrate therapeutic equivalence based on the provided *in vitro* data. The MAH also showed that the test and reference product are comparable with regard to crystalline (polymorphic) form, particle size distribution in suspension, pH, osmolality, density, viscosity, and extractable volume. As these parameters are comparable, it is expected that the test and reference product behave the same when the same nebuliser is used.

Packaging
The drug product is filled in low density polyethylene units. The single-dose units are packaged in foil laminate pouches. The primary packaging material is adequately characterized. It was shown that there are no toxicological concerns regarding extractables from the packaging.

Compatibility
The drug product is supplied as an aqueous suspension, thus no reconstitution diluents are required. The product is administered using a nebuliser, however Ultrasonic Nebulisers must not be used. The manufacturer of the finished product has been manufacturing unit dose inhalation products for administration using nebulisers for many years. The compatibility between the drug product and the dosage device has been established by the many years of marketing experience.

Manufacturing process
The manufacturing process includes preparation and sterile filtration of an excipient solution, the preparation and heat sterilisation of a drug concentrate, dispersion of the drug concentrate into the excipient solution, and filling and packing of the drug product suspension.
The batch sizes are acceptable based on the sizes of the batches used in the *in vitro* equivalence studies and the process validation data. The manufacturing process and in-process controls were sufficiently described with critical process parameters highlighted.
Process validation data have been provided for one batch per strength. The drug product is regarded as a specialised dosage form and the manufacturing process is regarded as non standard. Therefore, validation data on full scale batches should be provided. However, the provided validation data are considered sufficient due the fact that the three strengths differ only with regard to the concentration of the drug substance.

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

Quality control of drug product
The proposed drug product specification includes all tests required by the 'Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products', except for leachables. The latter have been extensively studied during pharmaceutical development. On the basis of the provided results, no test is required in the drug product specification. Release and shelf-life specifications differ with regard to the acceptance criteria for related substances. Identification by Infrared spectroscopy, content uniformity, and sodium chloride content are only tested at release, while appearance of secondary and tertiary pack and weight loss are only tested at shelf-life.
The product specifications cover appropriate parameters for this dosage form. The omission of tests for polymorphic form, particle shape and osmolality was justified. Batch analysis data of the three batches of each strength included in the *in vitro* equivalence study demonstrate compliance with the release specifications.

Stability of drug product
The stability studies were conducted under ICH conditions for products packed in semipermeable containers (low humidity conditions). Stability data is available up to 24 months at 25°C/40% RH and 6 months at 40°C/25% RH. Four full-scale batches of the 0.25 mg/2 ml strength, two full-scale and two pilot-scale batches of the 0.5 mg/2 ml strength, and three pilot-scale batches of the 1 mg/2 ml scale have been included. The tested parameters are considered to indicate stability sufficiently.
Apart from slight increases in impurity levels, no specific trends were observed in the provided stability data. Photostability of the drug product was tested under ICH conditions. The drug product was shown to be sensitive to light in the primary packaging while the secondary packaging protected the drug product sufficiently. The temperature cycling study showed that the drug product should not be frozen as large particles are formed.
On the basis of the provided stability data, the claimed shelf-life of 24 months is justified. In-use stability of opened pouches was studied during twelve weeks. No significant changes were observed during this period. The claimed in use shelf life of three months is justified.
The following storage conditions are applicable: "This medicinal product does not require any special temperature storage conditions. Do not freeze. Store in the upright position. Store the ampoule in the opened sachet. The opened sachet should be stored in the outer carton to protect from light and should not be frozen."

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 Budesonide Teva Steri-Neb 0.25 mg/2 ml, 0.5 mg/2 ml and 1 mg/2 ml, nebuliser suspension has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. Therapeutic equivalence is considered demonstrated based on the provided *in vitro* data.

The following post-approval commitments was made:
- The MAH committed to initiate long-term stability studies on product batches which have been held for the maximum holding time. Studies will be initiated for 0.25 mg/2 ml and 1 mg/2 ml product batches.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Budesonide Teva Steri-Neb is intended for 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 Pulmicort Respules, 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.

Ethylhexanol was identified as a potential leachate from the adhesive on the label of the ampoules. Ethylhexanol was detected up to 1.92 µg/ml. At this concentration, the maximum expected dose of ethylhexanol is 15.36 µg/day. This dose is far below the ADI of 0.5 mg/kg that was established by the WHO. No relevant risk is expected from the potential leachable ethylhexanol.

IV. CLINICAL ASPECTS

IV.1 Introduction

Budesonide 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/Pharmacodynamics

No pharmacokinetic or pharmacodynamic data have been provided. Bioequivalence based on systemic measurements of plasma concentration is generally not applicable for products that are intended for local use only without significant systemic absorption. The MAH refers to published pharmacokinetic and pharmacodynamic studies of (nebulised) budesonide. This is considered sufficient for this application.

IV.3 Clinical efficacy/safety

No clinical studies were submitted because the MAH claims that the comparative *in vitro* data generated comparing the formulation of Budesonide Teva Steri-Neb with the reference product, Pulmicort Respules, provide the proof of therapeutic equivalence.

Inhaled corticosteroids are established drugs in the treatment of bronchial asthma. Nebulised budesonide has been considered supplemental to the more common and simple inhaler devices, but may be of special importance for use in infants, children or adults with particularly poor inhalation technique.

The results of clinical literature and review studies demonstrate that nebulised budesonide is effective and safe. The safety and tolerability of nebulised budesonide has been demonstrated. Adverse events are well known and acceptable.

IV.4 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 Budesonide Teva Steri-Neb.

Summary table of safety concerns as approved in RMP

Safety concern	Description of routine risk minimisation activity
Systemic corticosteroid effects	Instruction to reduce the maintenance dose to the lowest possible effective dose in section 4.2 of the SmPC Instruction on the proper use of Budesonide Nebuliser Suspension in section 4.2 of the SmPC Warning in section 4.4 of the SmPC
Risks in switching patients from oral corticosteroids to inhaled corticosteroids	Warning in section 4.4 of the SmPC
Concurrent use of CYP3A inhibitors	Explanation in section 4.5 of the SmPC

Additional risk management activities are not required.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product. No new clinical studies were conducted. As Budesonide Teva Steri-Neb is a suspension for inhalation, it is exempted for biostudy. Essential similarity is demonstrated by comparative *in vitro* data only. This is acceptable and in line with the NfG CPMP/EWP/4151/00Rev.1 mentioning that for solutions for nebulisation that have the same qualitative and quantitative composition as the reference product, the requirement for clinical studies may be waived. The current product can be used instead of its reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Budesonide Arrow nebuliser suspension, registered through procedure DK/H/0703/001-003/MR. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Budesonide Teva Steri-Neb 0.25 mg/2 ml, 0.5 mg/2 ml and 1 mg/2 ml, nebuliser suspension from Teva Nederland B.V. have a proven chemical-pharmaceutical quality and are hybrid forms of name of Pulmicort 250, 500 and 1000 Respules, suspension for inhalation. Pulmicort Respules is a well-known medicinal product with an established favourable efficacy and safety profile

Since both the reference and current product are suspensions 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 Budesonide Teva Steri-Neb with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 October 2013.

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

Summary Public Assessment Report

non-generics

Budesonide Teva Steri-Neb 0.25 mg/2 ml, 0.5 mg/2 ml and 1 mg/2 ml, nebuliser suspension

(budesonide)

NL/H/2714/001-003/DC

Date: 5 August 2014

Summary Public Assessment Report

non-generics

Budesonide Teva Steri-Neb 0.25 mg/2 ml, 0.5 mg/2 ml and 1 mg/2 ml, nebuliser suspension
Active substance: budesonide

This is a summary of the public assessment report (PAR) for Budesonide Teva Steri-Neb nebuliser suspension. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Budesonide Teva Steri-Neb.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Budesonide Teva Steri-Neb and what is it used for?
Budesonide Teva Steri-Neb 0.25 mg/2 ml, 0.5 mg/2 ml and 1 mg/2 ml is a 'hybrid generic medicine'. This means that it is similar to a reference medicine containing the same active substance, Pulmicort 250, 500 and 1000 Respules, nebuliser suspension.
The active substance budesonide acts locally in the lungs, and is not absorbed in the body. This means that the levels in blood cannot be measured for direct comparison of Budesonide Teva Steri-Neb and Pulmicort Respules. This is why the term hybrid is used.

Budesonide Teva Steri-Neb is used in the treatment of asthma. It is used in patients where other types of inhaler, such as a pressurised inhaler or an inhaler containing a dry powder are unsatisfactory or inappropriate.

How does this medicine work?
The active substance budesonide belongs to a group of steroids called glucocorticosteroids. The main cause of asthma symptoms is inflammation of the airways. Budesonide is an anti-inflammatory agent. It works by reducing and preventing swelling and inflammation in the lungs.

How is this medicine used?
The medicine can only be obtained with a prescription. The pharmaceutical form of Budesonide Teva Steri-Neb is a suspension for nebulisation and the route of administration is by inhalation. This medicine must be used with a jet nebuliser. The "mist" produced is then inhaled through a mouthpiece or face mask. Ultrasound nebulisers should not be used with this medicine.
Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

How has this medicine been studied?
As this medicine is a locally active product, no bioequivalence could be performed. It is a suspension with the same composition of the active substance as the reference product. The excipients are common for this type of medicine. Because Budesonide Teva Steri-Neb was registered as a hybrid medicinal product and is considered to be therapeutically equivalent to the reference product Pulmicort Respules, their benefits and risks can be considered the same as those of the reference product.

What are the possible side effects from this medicine?
The most common side effects with this medicine (which may affect up to 1 in 10 people) are soreness and/or irritation in the mouth (including oral thrush), hoarseness, throat irritation, difficulty in swallowing and cough.

For the full list of all side effects reported with this medicine, see section 4 of the package leaflet.

Why is this medicine approved?
The Medicines Evaluation Board of the Netherlands decided that Budesonide Teva Steri-Neb's benefits are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Budesonide Teva Steri-Neb, 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 as well.

Other information about this medicine
The marketing authorisation for Budesonide Teva Steri-Neb 0.25 mg/2 ml, 0.5 mg/2 ml and 1 mg/2 ml, nebuliser suspension was granted on 29 January 2014.

The full PAR for this medicine can be found on the website http://mri.medagencies.org/Human. For more information about treatment with Budesonide Teva Steri-Neb, read the package leaflet (http://mri.medagencies.org/download/NL_H_2714_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in August 2014.