COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Azelastine/Fluticasonpropionaat STADA 137 microgram/ 50 microgram per actuation, nasal spray, suspension (azelastine hydrochloride and fluticasone propionate)

NL/H/5546/001/DC

Date: 7 February 2024

This module reflects the scientific discussion for the approval of Azelastine/Fluticasonpropionaat STADA 137 microgram/ 50 microgram per actuation, nasal spray, suspension. The procedure was finalised on 22 June 2023. 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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IVBE	*In vitro* bioequivalence study
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
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 quality, safety and efficacy data, the Member States have granted a marketing authorisation for Azelastine/Fluticasonpropionaat STADA 137 mg/ 50 mg per actuation, nasal spray, suspension from STADA Arzneimittel AG.

The product is indicated for: relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Dymista Nasenspray 137 Mikrogramm/50 Mikrogramm pro Sprühstoß Nasenspray, Suspension (NL RVG 114215) which has been registered in Germany by MEDA Pharma GmbH & Co. KG since 2013 (original product). In the Netherlands, Dymista Neusspray 137 microgram/50 microgram, neusspray, suspensie has been registered since 2014 by the procedure DE/H/3910/001/DC.

The medicinal product is a locally administered and locally acting (LALA) nasal spray, suspension for which bioequivalence with the reference product Dymista cannot be demonstrated through bioavailability studies. In vitro studies have been performed and demonstrated that the new product and the reference product have the same qualitative and quantitative composition and the same pharmaceutical properties (Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95), Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (CHMP/QWP/49313/2005 corr)).

The concerned member state (CMS) involved in this procedure was Germany.

Scientific advice was given by the RMS on 10 December 2020.

II. QUALITY ASPECTS

II.1 Introduction

Azelastine/Fluticasonpropionaat STADA is a white, homogeneous suspension and each gram of suspension contains as active substance 1,000 micrograms azelastine hydrochloride and 365 micrograms fluticasone propionate. One actuation (0.14 g) delivers 137 micrograms azelastine hydrochloride (125 micrograms azelastine) and 50 micrograms fluticasone propionate.

The excipients are: glycerol, microcrystalline cellulose (E460), carmellose sodium (E466), disodium edetate, polysorbate 80 (E433), benzalkonium chloride, phenylethyl alcohol and purified water.

The suspension is packed in a type I amber glass bottle fitted with a spray pump, a nasal polypropylene applicator (actuator) and a dust cap, containing 23 g (at least 120 actuations) suspension.

II.2 Drug Substance

Azelastine hydrochloride
The active substance is azelastine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is crystalline powder and is sparingly soluble in water. Azelastine hydrochloride exhibits optical isomerism with a possibility for a pair of optical isomers. The drug substance manufactured by the supplier(s) is a racemic mixture which is optical and inactive. Different polymorphic forms for azelastine hydrochloride have been described in the literature (hydrate, or different solvates from the anhydrous crystalline form). The anhydrous form is constantly manufactured by manufacturer(s), which is confirmed based on the IR, Xray diffraction and DSC studies. The drug substance is dissolved in the final drug product.

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
CEP(s) have 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. with additional requirements according to the CEP(s). Batch analytical data demonstrating compliance with this specification have been provided for six batches.

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

Fluticasone propionate
The active substance is fluticasone propionate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white

powder and is practically insoluble in water. For this product, a polymorphic form is consistently produced. Fluticasone propionate exhibits polymorphism and exists in two polymorphs, based on literature. The active ingredient provided by selected manufacturer(s) is stable form I. Form II is obtained only with a specific technique, thus no transformation is expected during product manufacturing. Fluticasone propionate is optically active with nine chiral centres. During synthesis no reaction occurs at the chiral centres thus ensuring that fluticasone propionate exists as single isomer.

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

CEP(s) have 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. with additional requirements for residual solvents conform the CEPs. Batch analytical data demonstrating compliance with this specification have been provided for eleven batches.

Stability of drug substance

The active substance is stable for at least two 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 applicant has executed a formal *in vitro* BE (IVBE) study between the proposed test product and reference product (Dymista, Meda Pharmaceuticals) as a valid surrogate for comparative *in vivo* pharmacokinetic/clinical therapeutic equivalence studies. Reference is made to EMA Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005 Corr) and FDA draft guideline on bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action for nasal products. No new *in vivo* PK studies were performed. The statistical evaluation was based on average bioequivalence methods as recommended in EMA guideline on the requirements for clinical documentation for orally inhaled product (OIP).

In vitro bioequivalence study (IVBE)

For nasal sprays that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and the extent to which the active ingredient or active moiety becomes available at the site of action. The following parameters have been identified as relevant for evaluation of therapeutic equivalence of test and reference product by *in vitro* studies, i.e.:

- Similarity of composition
- Total delivered dose which is controlled by parameters as mean delivered dose and delivered dose uniformity
- Similarity of dissolution of active substance at site of action, which is controlled by particle size distribution of fluticasone propionate, polymorphic form and physicochemical properties (pH, Viscosity, osmolality, zeta potential).
- Device part similarity
- Deposition pattern in the nose (location and area) controlled by parameters DSD and small droplets. Droplets with size <10 µm are to be avoided for safety reasons as they are likely to reach the lungs.

Overall conclusion IVBE study

Three industrial scale batches of test and reference product of different countries and age were assessed in the IVBE study. Single actuation content (SAC), droplet size distribution, and prime and re-priming was performed for each batch of the test and reference product at the beginning and end of the container life for each unit. The 90% confidence interval of the geometric means ratio of delivered dose of the test product versus the reference product of the parameters lies within the BE acceptance limits of 80-125% which demonstrates equivalence between the test and reference product.

Manufacturing process

The manufacturing process includes preparation of a solution of azelastine hydrochloride in a mixture, preparation of excipients and addition of a pre-mix (suspension) of fluticasone propionate, followed by filtration and filling/crimping.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three industrial scale batches at the lower border of the batch size, in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. requirements except for phenylethyl alcohol which complies with USP-NF requirements. These specifications are acceptable.

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, identification of drug substance, identification of benzalkonium chloride, phenylethyl alcohol and EDTA, assay of drug substance, related substances and total impurities of azelastine hydrochloride, related

substances and total impurities of fluticasone propionate, mean delivered dose, delivered dose uniformity, number of actuations per container, assays of benzalkonium chloride, phenylethyl alcohol and EDTA, droplet size distribution, pH, viscosity, and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three industrial scale batches from the production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three industrial scaled batches stored at 25°C/60% RH (24 months), 30°C/75% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. No significant changes were seen during the 6 months accelerated, intermediate and long-term stability study for most of the tested parameters except for the assay of two excipients where slight decreasing trends were seen. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are do not refrigerate or freeze.

In-use stability data have been provided demonstrating that the product remains stable for 6 months following first opening of the container, when stored at 30°C/75% RH in horizontal storage position, both initially and after 18 months long term storage.

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 Azelastine/Fluticasonpropionaat STADA 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 Azelastine/Fluticasonpropionaat STADA is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Dymista Nasenspray which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

No clinical pharmacokinetic studies or additional clinical studies for efficacy and safety were performed, as the MAH claims therapeutic equivalence based upon *in vitro* data.

IV.2 Pharmacokinetics

No bioequivalence study was performed as the MAH claims therapeutic equivalence based upon *in vitro* data comparing Azelastine/Fluticasone propionate Nasal Spray with the reference product Dymista Nasenspray. Azelastine/Fluticasonpropionaat STADA propionate Nasal Spray is a locally administered and locally acting nasal spray, suspension formulation. Extensive clinical experience with azelastine/fluticasone propionate is considered to have demonstrated therapeutic value of this fixed-dose combination for the relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis in adults and adolescents, if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient. The indicated population for this application is identical to that of the innovator: adults and adolescents (12 years and older).

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 Azelastine/Fluticasonpropionaat STADA.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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 Dymista. No new clinical studies were conducted. The MAH demonstrated through *in vitro* studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This 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 with 2 participants, followed by two rounds with 10 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

Azelastine/Fluticasonpropionaat STADA 137 mg/ 50 mg per actuation, nasal spray, suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Dymista Nasenspray 137 mg/ 50 mg, neusspray, suspensie. Nasenspray is a well-known medicinal product with an established favourable efficacy and safety profile.

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

Azelastine/Fluticasonpropionaat STADA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 June 2023.

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
-	-	-	-	-	-