COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pollinex grass pollen initial course and extension course, suspension for injection in vial 300, 800 and 2000 SU/0.5 ml
Pollinex grass pollen initial course, suspension for injection in vial 300, 800 and 2000 SU/0.5 ml
Pollinex grass pollen extension course, suspension for injection in vial 2000 SU/0.5 ml

(grass pollen)

NL RVG License 125188-125190

Date: 9 February 2021

This module reflects the scientific discussion for the approval of Pollinex grass pollen initial course and extension course, suspension for injection in vial 300, 800 and 2000 SU/0.5 ml. The procedure was finalised at 28 July 2020. 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Pollinex grass pollen initial course and extension course, suspension for injection in vial 300, 800 and 2000 SU/0.5 ml, from Allergy Therapeutics Netherlands BV.

The product is indicated for the treatment of rhino conjunctivitis and/or allergic asthma in adults, adolescents and children from 6 years of age caused by an allergy to grass pollen. The diagnosis must be medically confirmed before determining the indication.

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

This procedure concerns a line-extension to obtain marketing authorisation for vials in addition to the already authorised Pollinex initial course and extension course 300, 800, 2000 SU/0.5 ml, suspension for injection in a pre-filled syringe (RVG 121895-121897). Whereas the pre-filled syringes are single-use containers, the vials are multi-use containers allowing 2 or 3 doses per vial.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC, a full application.

II. QUALITY ASPECTS

II.1 Introduction

Pollinex is a white opaque suspension for injection. The product contains 12 different grass pollen that are converted into allergoids by treatment with glutaraldehyde and are adsorbed onto the amino acid L-tyrosine. The allergen extracts are characterised and standardised (in SU, Standardised Units) through immunological and biochemical methods to ensure batch-to-batch consistent allergen content and allergenic potency.

- RVG 125188 - Pollinex grass pollen initial course and extension course, suspension for injection in vial 300, 800 and 2000 SU/0.5 ml
- RVG 125189 - Pollinex grass pollen initial course, suspension for injection in vial 300, 800 and 2000 SU/0.5 ml
- RVG 125190 - Pollinex grass pollen extension course, suspension for injection in vial 2000 SU/0.5 ml

The suspension for injection is packed in sterile, transparent, glass vials fitted with a chlorobutyl rubber stopper with aluminium crimp cap with tamper evident 'flip top' plastic cover.

The excipients are: L-tyrosine, sodium chloride, phenol, glycerol, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections.

II.2 Drug Substance

The drug substance is a native aqueous extract from equal amounts of 12 grass pollens, in a buffer solution (Evans solution). The common and scientific names for the pollens are listed in table 1 below.

Table 1. Grass pollen mix used in the manufacture of the drug substance

Common Name	Scientific name
Bent grass	*Agrostis capillaris/tenuis*
Foxtail (meadow)	*Alopecurus pratensis*
Sweet Vernal	*Anthoxanthum odoratum*
False Oat	*Arrhenatherum elatius*
Brome	*Bromus spp.*
Crested Dogstail	*Cynosurus cristatus*
Cocksfoot (Orchard grass)	*Dactylis glomerate*
Fescue (Meadow)	*Festuca pratensis*
Yorkshire Fog	*Holcus lanatus*
Rye grass	*Loliom perenne/multiflorum*
Timothy grass	*Phleum prantense*
Meadow grass	*Poa pratensis/trivialis*

The drug substance is an aqueous solution containing native allergens, gained by extraction of 12 grass pollens. Each individual grass pollen type is of biological origin and as such the 12-grass aqueous extract (drug substance) does not constitute an active principle corresponding to a defined molecule. Rather, the extract consists of a mixture of proteinaceous molecules, some of which have enzymatic properties. However, the source of the drug substance is well defined and reproducible in nature; proteins are readily extracted from the pollens.

Manufacturing process

The manufacturing process consists of extraction of the pollens, purification by clarification/filtration, dialysis and further clarification, filtration and analysis. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

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. for allergen products. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The drug substance material is not stored during the manufacturing process. The manufacturing process is a continuous process to the medicinal product. Therefore, stability data on the drug substance are not applicable.

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 line extension was submitted to seek marketing authorisation for the presentation in vials instead of pre-filled syringes. For the other aspects the product is the same as the approved syringe presentation. No clinical studies or bioavailability or bioequivalence studies are required for the proposed product as cross-reference is made to the non-clinical and clinical data approved for the existing product Pollinex in pre-filled syringes.

Manufacturing process

No change has been made to the manufacturing process other than the change of final presentation (vials instead of syringes). The manufacturing process is considered acceptable.

Control of excipients

The excipients are the same as in the pre-filled syringe presentation and comply with Ph. Eur. These specifications are acceptable.

Quality control of drug product

The finished bulk and filled product specifications are adequate to control the relevant parameters for the dosage form. The specifications include tests for description, pH, excipient content, uniformity of suspension, dye absorption ratio, identity, allergen content, protein nitrogen, filling volume, seal integrity, sterility, protein content and endotoxin. 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. The relevant specifications are in line with those for the pre-filled syringes. Moreover, an assay to determine lack of IgE activity (allergen content of supernatant) is in place. Batch analytical data of three 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 for four batches per strength stored at 5°C±3° (up to 36 months). On the basis of the data submitted, a shelf life was granted of 3 years when stored in a refrigerator (2°C-8°C). The product cannot be stored in a freezer. The provided process validation data, batch data and stability data are largely from the 13 grass suspension for injection filled vials licensed in other countries, which are very similar having cultivated rye pollen extra to the pollen present in the 12 grass product. The MAH has committed to providing the full validation data for the 12 grass product post-approval.

Data were provided for 13 grass Pollinex for a total of 5 interventions over a 30 week period. These data support the in-use period (10 weeks with less interventions) of 12 grass Pollinex vials.

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 MEB considers that Pollinex has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitments was made:

- The MAH has committed to providing full validation data for 12 Grass filled vials to complete the validation data to three batches for each strength. The final validation report will be provided no later than 31 December 2021.
- Specification limits for quantification of Group 5 allergen will be introduced based on three batch data following formal variation application to include the quantification of group 5 allergens. Formal variation application will be submitted upon completion of the manufacturing and process validation studies by the end of 2021.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00) vaccines are exempted from the requirement for an environmental risk assessment due to the nature of their constituents.

III.2 Discussion on the non-clinical aspects

This product is a line extension of the previous approved Pollinex product in pre-filled syringes. No new non-clinical data have been submitted. Therefore, the application has not undergone additional pre-clinical assessment, which is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.1 Introduction

For this application reference is made to the clinical data of Pollinex initial course and extension course 300, 800, 2000 SU/0.5 ml, suspension for injection in a pre-filled syringe. No new clinical studies have been performed.

IV.2 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 Pollinex.

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

Important identified risks	- Anaphylaxis/Anaphylactic shock
Important potential risks	- Overdose/medication error
Missing information	None

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the already approved product Pollinex initial course and extension course 300, 800, 2000 SU/0.5 ml, suspension for injection in a pre-filled syringe. No new clinical studies were conducted. Risk management is adequately addressed.

V. USER CONSULTATION

A common patient leaflet for the 6 presentations (3 original and 3 newly added products) is proposed, which is based on the approved leaflet for the pre-filled syringes (RVG 121895/6/7) to which minor product specific additions have been made for the additional vial presentations. As these additions in the leaflet do not affect the readability, a readability testing report is not included in this application. This is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pollinex grass pollen initial course and extension course, suspension for injection in vial 300, 800 and 2000 SU/0.5 ml have a proven chemical-pharmaceutical quality and are a legitimate line extension to Pollinex initial course and extension course 300, 800, 2000 SU/0.5 ml, suspension for injection in a pre-filled syringe. Pollinex is a well-known medicinal product with an established favourable efficacy and safety profile.

No new non-clinical or clinical studies were conducted. Risk management is adequately addressed.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pollinex with the previously authorised product in pre-filled syringed, and has therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 28 July 2020.

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