CBG MEB

Public Assessment Report

Scientific discussion

Xelf Xylometazoline HCl Menthol 1 mg/ml, nasal spray, solution

(xylometazoline hydrochloride)

NL License RVG: 116566

Date: 13 March 2018

This module reflects the scientific discussion for the approval of Xelf Xylometazoline HCl Menthol 1 mg/ml, nasal spray, solution. The marketing authorisation was granted on 3 December 2015. 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
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 Xelf Xylometazoline HCl Menthol 1 mg/ml nasal spray, solution, from Basic Pharma Manufacturing bv.

The product is indicated for the treatment of nasal congestion.

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

This national procedure concerns a hybrid application claiming essential similarity with the innovator product Otrivin XylometazolineHCl Menthol 1 mg/ml nasal spray (NL License RVG 18445). Otrivin nasal spray 1 mg/ml was first registered in the Netherlands by GlaxoSmithKline Consumer Healthcare B.V. in 1996.

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

II. QUALITY ASPECTS

II.1 Introduction

The drug product is a 1 mg/ml xylometazoline hydrochloride nasal spray solution. It consists of 1 mg/ml xylometazoline hydrochloride. Each delivered dose contains 140 microgram xylometazoline hydrochloride, which corresponds to 121.7 microgram xylometazoline.

The product is packed in a 10 ml brown glass bottle with polyethylene (PE) spray pump with polypropylene (PP) cap.

The excipients are benzalkonium chloride, levomenthol, cineole, disodium edetate dihydrate, sodium dihydrogenphosphate dihydrate, disodium hydrogenphosphate dodecahydrate (E339), sodium chloride, macrogolglycerol hydroxylstearate, and purified water.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

II.2 Drug Substance

The active substance is xylometazoline hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, crystalline powder. Xylometazoline hydrochloride is freely soluble in water, in ethanol (96%) and in methanol.

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. and the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
The active substance is stable for 48 months 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 qualitative and quantitative composition of Xelf Xylometazoline HCl Menthol 1 mg/ml, nasal spray solution is based on a marketed product from the same authorisation holder with the addition of levomenthol and eucalyptol. The antimicrobial efficacy was investigated during product development. Due to a difference in composition between the test (absence of sorbitol, higher concentration of eucalyptus oil and menthol) and reference product a justification has been provided that the difference is of no concern regarding safety, efficacy and quality. This has been substantiated by comparing pH, surface tension, viscosity, osmolality, buffer capacity, dose weight, droplet size distribution, spray pattern and fraction of droplets smaller than 10 µm between the test and reference product. Two spray pumps have been suggested for the proposed product. These parameters have been investigated for both spray pumps. No significant differences have been observed. The pharmaceutical development of the product has been adequately performed.

The drug product is a locally acting locally applied product. No clinical studies have been performed. Therapeutic equivalence based on pharmaceutical equivalence can be accepted based on the outcome of the parameters that have been investigated.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. 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 appearance, of the container and the content, colour, clarity, odour, pH, relative density, identification, assay, uniformity of content of bottles, average volume of the bottles, dosage volume, related substances, microbiological purity, number of actuations and droplet size distribution. The release and shelf life limits are identical with the exception of the related substances. 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 production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for three production scaled batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. At long term, intermediate and accelerated conditions out of specification results were observed for number of actuations. A clarification is provided and the incoming goods inspection has been adjusted.

An in use shelf life was performed up to four weeks after 12 months of storage at long term conditions. The number of actuations was not included as tested parameter in this study.
Based on the provided data a shelf life of 24 months in the proposed packaging with storage condition: Store below 25°C and an in use shelf life of one month can be granted.

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 Xelf Xylometazoline HCl Menthol 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 Xelf Xylometazoline HCl Menthol 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 Otrivin 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

Biowaiver

No comparative bioavailability studies have been conducted to support the application. Essential similarity with the originator product is based on comparative qualitative attributes of the product. The Guideline on requirements for locally applied, locally acting products, containing known constituents (CPMP/239/95) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed.

The composition of the test product and the innovator product differs with respect to the excipients sorbitol, eucalyptus oil, menthol and macrogolglycerol hydroxylstearate:

- *Sorbitol* - the absence of sorbitol in the test product is sufficiently clarified.
- *Menthol* - as far as the systemic safety concerned, the higher amount of menthol in the test product is considered safe, as addressed by the WHO for use as food additives. However, regarding local safety and tolerance, menthol may cause mucosal and skin irritation. The mucous membranes of the nose can be more vulnerable, when irritated or inflamed. In such a situation, a higher concentration of menthol may have a greater impact on the safety. The provided non-clinical data did not provide additional information to address the safety concern.
  The MAH deduced the safety of their own product with the higher amount of menthol from the safety of the originator in combination with the suggested large safety margin observed in animal studies. As in the Swedish PAR of Otrivin Menthol (with preservative) a large safety margin for menthol is considered plausible the local tolerability is considered sufficiently addressed.
- *Eucalyptol* - to support the safety of the higher concentration of eucalyptus oil in the test product, the MAH refers to the published Assessment report on Eucalyptus globulus Labill folium. Altogether, it is considered that the local tolerance is sufficiently addressed.
- *Macrogolglycerol hydroxylstearate* - the test product contains a lower concentration macrogolglycerol hydroxylstearate. This is accepted as it is unlikely that macrogolglycerol hydroxylstearate in this concentration affects the solubility and absorption of xylomethazoline.

The physic-chemical parameters are comparable or acceptable, including pH, surface tension, viscosity and iso-osmotic value. Also comparative batch analytical data demonstrated that appearance, content, colour, clarity, odour, pH, relative density, assay of xylometazoline, benzalkonium chloride and disodium edetate, one specified impurity, any other single impurity, total impurities, spray volume and droplet size distribution are similar for both spray pumps and comparable with the innovator product.

Since the product is similar to that of the reference product Otrivin XylometazolineHCl Menthol 1 mg/ml nasal spray and the pharmaceutical properties are comparable to that of the reference product as well, a biowaiver can be granted. Xelf Xylometazoline HCl Menthol may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product.

IV.1 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 Xelf XylometazolineHCl Menthol.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Rebound congestion
Important potential risks	• Misuse • Overdose • Long term use (more than seven days) • Lack of efficacy in children aged 2-12 years
Missing information	--

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

IV.2 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Otrivin XylometazolineHCl Menthol 1 mg/ml nasal spray. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Xelf Xylometazoline HCl 1 mg/ml nasal spray. The only difference in the PL between the Xylometazoline-version and the Xylometazoline Menthol-version concerns the listing of three additional excipients (levomenthol, cineole and macrogolglycerol hydroxystearate). The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Xelf Xylometazoline HCl Menthol 1 mg/ml, nasal spray, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Otrivin XylometazolineHCl Menthol 1 mg/ml nasal spray. Otrivin XylometazolineHCl Menthol is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence between Xelf Xylometazoline HCI Menthol and the reference formulation Otrivin XylometazolineHCl Menthol has been established.

In the Board meeting of 26 November 2015, the menthol and eucalyptol concentrations in the test product were discussed: The MEB considers that the local safety and tolerability of menthol and eucalyptol is sufficiently substantiated.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Xelf Xylometazoline HCI Menthol was authorised in the Netherlands on 3 December 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Transfer of MAH	IB	28-12-2015	11-02-2016	Approval	
Transfer of MAH	IB	13-04-2016	17-05-2016	Approval	
SmPC update due to extension of shelf life to 24 months	IB	22-07-2016	15-08-2016	Approval	
Update of CEP of already approved manufacturer and new CEP of new manufacturer.	IA	29-03-2017	14-04-2017	Approval	