CBG MEB

Public Assessment Report

Scientific discussion

Xylomare 0.5 mg/ml and 1 mg/ml, nasal spray, solution

(xylometazoline hydrochloride)

NL/H/3713/001-002/DC

Date: 12 April 2019

This module reflects the scientific discussion for the approval of Xylomare 0.5 mg/ml and 1 mg/ml, nasal spray, solution. The procedure was finalised on 21 June 2017. 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
CNS	Central Nervous System
CVS	Cardio Vascular System
ECG	Electrocardiography
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
LD50	Lethal dose for 50% of subjects
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 Xylomare 0.5 mg/ml and 1 mg/ml, nasal spray, solution from Healthypharm B.V.

The product is indicated for the temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis

The 0.5 mg/ml strength is intended for children between ages 2 and 12 years. The 1 mg/ml strength is intended for children from 12 years of age and for adults.

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

The active substance xylometazoline is well-known and it has been used in the EEA in the treatment of nasal congestion caused by rhinitis/sinusitis since 1959. The innovator product Otrivin nasal spray 1 mg/ml was first registered in the Netherlands by Novartis consumer health in 1978. Reference is made to Otrivin authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Denmark, Spain, Italy (only the 1 mg/ml strength) and Poland (only the 1 mg/ml strength).

The application is based on article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of xylometazoline hydrochloride.

Indication
The initial indications applied for were "*for detumescing the nasal mucosa in the event of colds and attacks of runny colds (vasomotor rhinitis), allergic rhinitis*" and "*for facilitating the flow of secretion in inflammation of the paranasal sinuses as well as in catarrh of the tubal middle ear associated with colds*". During the application procedure the indication has been adapted to *"Temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis"*.

II. QUALITY ASPECTS

II.1 Introduction

Xylomare is a clear, colourless nasal spray, solution with a pH range from 5.5 to 6.5 and osmolality of 240 to 330 mOsmol.

Xylomare 0.5 mg/ml nasal spray, solution
1 ml of nasal spray, solution contains 0.5 mg xylometazoline hydrochloride. Each spray (of approx. 0.09 ml of solution) contains 0.045 mg xylometazoline hydrochloride.

Xylomare 1 mg/ml nasal spray, solution
1 ml of nasal spray, solution contains 1 mg xylometazoline hydrochloride. Each spray (of approx. 0.09 ml of solution) contains 0.09 mg xylometazoline hydrochloride.

The solution is packed in polyethylene bottle with a spray pump system (3K-pump-system or a PFP N pump system) of polyethylene and polypropylene.

The excipients are potassium dihydrogen phosphate, purified sea water and purified water.

II.2 Drug Substance

The active substance is xylometazoline hydrochloride, a well-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.

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. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance
The active substance is stable for four 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 development of the product has been described. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

The MAH initially performed an *in vitro* comparison to Otrivin 0.1% Dosierspray ohne Konservierungsmittel, to provide a bridge between the literature provided, to substantiate efficacy and safety, and the product applied for. Both products are preservative free. However the composition of the reference product and the test product are not similar. Xylomare contains the following excipients: seawater, potassium dihydrogen phosphate and purified water. The reference product contains sodium chloride, sodium monohydrogen phosphate dodecahydrate, sodium edetate and purified water.
Sufficient information concerning the possibility for therapeutic enhancement or impairment of the active ingredient and safety has been provided. The excipients are common excipients for nasal sprays. Sea water is used as an excipient (with the purpose to obtain isotonic conditions) in EU approved nasal sprays with the same use and indications and consequently there is no objection to its use in the test product.

Manufacturing process
The manufacturing process consists of bulk manufacture, sterile filtration and filling and is performed under aseptic conditions. 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 per strength in accordance with the relevant European guidelines.

Control of excipients
Except for sea water, the excipients comply with Ph.Eur. requirements. An in-house specification for sea water is provided, based on Directive 89/83/EC. 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 and includes tests for appearance, pH, osmolality, relative density, uniformity

of mass of one dosage unit, mean delivered mass of the spray shot, number of actuations per container, identification, assay, related substances and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Droplet size distribution will be included in the drug product specification by an applicable variation procedure post approval.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scale batches per strength 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 on at least three full scale batches per strength batches stored at 25°C/65% RH (12-60 months) and 40°C/75% RH (6 months). Some of the batches are also stored at 30°C/60% RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. No significant changes are observed at either condition. On the basis of the data submitted, a shelf life was granted of 60 months for the unopened product and 12 months after first opening (in-use period). Photostability testing shows that the finished product is not sensitive to 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 Xylomare has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- A variation application will be made to include a release and shelf life specification for droplet size distribution. In case stability samples will be available, the test will be performed at the end of the ongoing studies.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Xylometazoline was found to bind to all alpha-adrenoceptor subtypes with the highest affinity for the alpha-adrenoceptor α2B. Application of xylometazoline causes a vasoconstriction due its α-adrenoceptor agonistic action. In addition, xylometazoline was shown to concentration dependently inhibit both forms of nitric oxide synthase, the inducible and the constitutive form, and to inhibit more efficiently the induction of this enzyme than the activity of nitric oxide synthase (Westerveld et al., 2000). Nitric oxide (NO) is an important mediator in modulating the inflammatory and immunological response in upper respiratory tract.

Local decongestant activity of xylometazoline has been demonstrated *in vitro* and in animal models. Xylometazoline efficiently reduced nasal mucosal swelling and nasal resistance in dogs (Jackson and Birnbaum, 1981; 1982). A concentration-dependent decrease of the sinus mucosal blood flow was seen after the application of xylometazoline to rabbits (Bende et al., 1993). Xylometazoline was shown to reduce the tension of the Eustachian tube thus facilitating tube opening (Svane-Knudsen et al., 1982).

Xylometazoline administered systemically affected heart function and circulation in studies in dogs. It significantly increased the cardiac force of contraction, the perfusion pressure and blood pressure, and slightly reduced heart rate (Walkenhorst et al., 1981). Tachycardia, palpitations, hypertension, headache, and cardia arrhythmias are cardinal symptoms of an acute decongestant toxicity (Balbani et al., 2000). Xylometazoline increased coronary resistance in both the isolated and in the in-situ heart

(Ertl and Fuchs, 1980). Data confirming cardiovascular effects of xylometazoline following nasal application are not available.

Data on xylometazoline effects on central nervous system following nasal application of the recommended dose are not available. However, no effects are expected following correct application. The clinical picture of intoxication with xylometazoline may consist of phases of stimulation and phases of inhibition of the central nervous (CNS) and cardiovascular (CVS) system.

Xylometazoline inhibited neutrophil and granulocyte function *in vitro* indicating possible adverse effects on immune function (Hakansson et al., 1989a; 1989b).

III.2 Pharmacokinetics

Relatively little data are available on pharmacokinetic studies in animals and humans. Information on the kinetics in animals (rat and dog) was obtained with 14C-labelled xylometazoline following oral and intravenous doses. Xylometazoline was completely absorbed following oral administration of 14C-xylometazoline to rats or dogs. Major target organs for distribution after intravenous (IV) administration were heart, lungs, adrenal gland, thyroid, salivary glands, kidney, pancreas and liver. Elimination half-life was 1.85 hours in dogs following IV administration and, 72 hours after oral administration, no 14C-xylometazoline was detectable (Aufbereitungskommission Xylometazolin-Monografie, 1994). In humans no systemic absorption is expected following topical application of the medicinal product. Following nasal application of the solution, local vasoconstriction usually occurs within 5-10 minutes and persists for up to 12 hours (Aufbereitungskommission Xylometazolin-Monografie, 1994; Chua et al., 1989).

III.3 Toxicology

LD50 values, depending of the route of application, were 22-210 mg/kg for the mouse, 3-154 mg/kg for the rat, and 30 mg/kg for the dog (oral administration). Symptoms observed at sub lethal doses were e.g. difficulty to breath, reduction in the spontaneous motility, ataxia, arrhythmias, tremor, tonic-clonic convulsions, and hyperreflexia (Aufbereitungskommission Xylometazolin-Monografie, 1994) Xylometazoline was less toxic than ephedrine in mice and rabbits. Clinical signs of toxicity were typical sympathomimetic effects, such as mydriasis, pilomotor excitation, tachycardia and hypertension (Kolodny, 1959). Doses of 6, 20, and 60 mg/kg for three months to rats resulted in hypertension, reduced food intake, and dose-dependent body weight gain. No pathological findings were found in the low-dose group, while animals of the higher dose groups showed slight changes associated with hypertension (Aufbereitungskommission Xylometazolin-Monografie, 1994). Repeated nasal application of xylometazoline to dogs did not result in any relevant toxicity (SmPC Otrivin). Systemic administration of xylometazoline 1, 3, and 10 mg/kg resulted in slight dose-dependent signs of toxicity such as reduced food intake, reduction in body weight. Changes in ECG occurred in all dose groups, mortality only at the higher dose levels (Aufbereitungskommission Xylometazolin-Monografie, 1994). A current data search in toxicological databases did not reveal new evidence of repeated-dose toxicity of xylometazoline.

Xylometazoline was not genotoxic *in vitro* and *in vivo*. Although no preclinical carcinogenicity study is available, there is no evidence of any carcinogenic potency based on genotoxicity study results.

No effects on fertility and no teratogenic effect of xylometazoline were detected in rats and rabbits, but dose levels exceeding the therapeutic range caused embryo mortality or reduced foetal growth.

The most important issue for the current product regarding toxicity is local tolerance. Various authors have reported ciliotoxicity of topical nasal medications; however, it is sometimes difficult to dissociate the effects of the active substance from that of the preservative. Cytotoxicity, in particular decreases in ciliary beat frequency and reduced cell growth, was observed for xylometazoline. Xylometazoline product containing preservatives were more toxic than products without preservatives. As the product does not contain any preservatives, it is unlikely that there will be any new or exaggerated toxic effects, other that the effects already known for xylometazoline.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Xylomare is intended for substitution of other nasal sprays containing xylometazoline already on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

The application for Xylomare is based on well-established use. This is endorsed, since xylometazoline hydrochloride has been registered for this indication for a long time (in the Netherlands since 1978) and the dose is not increased. 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

Xylometazoline hydrochloride 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

No human pharmacokinetic data are available for xylometazoline hydrochloride after nasal application.

Absorption
There is only minimum systemic absorption of xylometazoline when it is used in the recommended dose and route of administration. Failure in the administration technique or in the administered dose may result in systemic absorption and adverse effects.

Distribution, protein binding
Data on distribution and protein binding of xylometazoline are not available.

Metabolism
Data on metabolism of xylometazoline in humans are not available.

Elimination
Data on elimination of xylometazoline are not available. However, renal elimination of xylometazoline appears to occur if systemic availability of xylometazoline is suspected, e.g. after an overdose. Following accidental administration of a 2% solution to three small children, the following xylometazoline concentrations in urine were found: child 1: 6.6 mg/l, child 2: 2.1 mg/l, and child 3: 1.7 mg/l.

Pharmacokinetics in special populations
Data on pharmacokinetics of xylometazoline in special populations are not available.

Interaction
During the procedure the applicant substantiated that the interactions between xylometazoline with monoamine oxidase inhibitors, tricyclic or tetracyclic antidepressants can result in increase in blood pressure, especially in case of overdose. The possible interaction with β-blocker was also described.

IV.3 Pharmacodynamics

There is no information on the nasal dose-relationship with the decongestant effect of xylometazoline. The MAH proposed to use the dose of 0.05% for children 2-12 years and 0.1% for adults and children ≥12 years. This is accepted as it in line with current EU applications.

IV.4 Clinical efficacy

Short term use of xylometazoline hydrochloride in the alleviation of nasal congestion is well established. Xylometazoline hydrochloride provides a rapid decongestant effect with a decrease in nasal airflow resistance and increase of inspiratory flow. It appears to be effective and well tolerated and provide long lasting relief of nasal congestion and is well established in the temporary symptomatic relief of nasal congestion.

Indication
The MAH originally also applied for an indication which refers to facilitating of secretions of the paranasal sinus or middle ear tube, however this indication was not considered well-established as it is not included in the Dutch innovator product Otrivin nor widely accepted in the EU, consequently this indication was removed during the procedure.

Additional studies have been provided to support the indication in children aged 2-12 years and adolescents. The provided literature applied for children age 2-12 is sparse for the applied application. The pivotal study to support the application has been conducted in children aged 6-12 years (Michel et al., 2005). In the pivotal study a total of 70 patients aged 2-6 years with acute rhinosinusitis were included. The primary aim of the study was to determine the effectiveness of a topical treatment of natural mineral salts or xylometazoline (0.05%) after a 14 day treatment in a randomised double blind controlled cross over study. Both treatments showed an improvement in symptoms at the end of treatment.
Other provided studies have been regarded as supportive because they were conducted in other indications: the prevention of epitaxis in nasal intubation (El-Seify et al., 2010), discomfort by nasendoscopy (McCluney et al., 2009; Chadha et al., 2013), and diagnostic determination of need of surgical intervention (Zicari et al., 2012).
The use of xylometazoline in children is well established as it is mentioned for as a nasal congestant in the position paper of the European Academy of Allergy and Clinical Immunology (Roberts et al., 2013).
The overall provided data supports the well established use of the 0.5 mg/ml strength for children between 2-12 years.

IV.5 Clinical safety

Nasal xylometazoline has a well characterised safety profile. Human safety data have been generated in clinical trials and systematically through post marketing pharmacovigilance. The nasal related side effects are generally mild to moderate. Intranasal use of xylometazoline has been associated with local burning, stinging, sneezing and dryness of the nasal mucosa. Long-term use can cause nasal stuffiness and tolerance (rhinitis medicamentosa).

The most frequently reported non-nasal adverse event is headache. If used as directed, xylometazoline is not expected to lead to severe systemic effects.
Palpitations have been infrequently observed. After overdose, significant cardiovascular effects may occur, including hypertension and arrhythmias. Nausea and vomiting have rarely been reported.
Xylometazoline is capable of depressing the CNS, with drowsiness and profound CNS depression occurring after excessive doses in children. Reports on adverse events in younger children (below six years) are related to accidental ingestion (https://www.fda.gov/Drugs/DrugSafety/ucm325257.htm) or off-label use (Latham and Jardine, 2013) of nasal decongestant sprays.

Xylometazoline can be used with or without preservatives. Patients who received nasal decongestant without a nasal preservative tolerated the treatment better as they reported less frequent the feeling of dryness of the nose (Dorn et al., 2013).

Excipients
Excipients are usually included for bulking up formulations, but they may also confer to therapeutic enhancement or impairment of the active ingredient. They should be well tolerated if locally applied. The originally submitted dossier did not contain sufficient information concerning this possibility for therapeutic enhancement or impairment of the active ingredient and (local) safety. During the procedure the MAH sufficiently updated the dossier with this information; these excipients are

common excipients for nasal sprays. It is also acknowledged that (diluted) sea water is used as an excipient (with the purpose to obtain isotonic conditions) in EU approved nasal sprays with the same use and indications and consequently there is no objection to its use in the product applied for.

IV.6 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 Xylomare.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Rebound nasal congestion, reactive hyperaemia or atrophy of nasal mucosa following long-term use • Overdose
Important potential risks	--
Missing information	--

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

IV.7 Discussion on the clinical aspects

Xylomare is considered widely established. For this authorisation, reference is made to clinical studies and experience with xylometazoline hydrochloride. Xylometazoline hydrochloride has been shown to be effective in the temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis. The provided clinical overview is sufficient. No new clinical studies were conducted. This is accepted.

V. USER CONSULTATION

The package leaflet has (PL) 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 three participants, followed by two rounds with ten 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Xylomare 0.5 mg/ml and 1 mg/ml, nasal spray, solution has a proven chemical-pharmaceutical quality. Xylomare is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

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 Xylomare with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 June 2017.

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
Change in the (invented) name of the medicinal product in NL, IT, PL, and ES. Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use	NL/H/3713/IB/001/G	IB	23-2-2018	25-3-2018	Approved	--
Addition of bulk manufacturer and primary packager for a sterile medicinal product Addition of secondary packager Addition of new test method for in-process controls Change in batch size of the finished product	NL/H/3713/IB/002/G	IB	18-10-2018	9-11-2018	Approved	--
Change in container closure system specification with regard to the composition of pump materials Change in the name of a supplier of a packaging component	NL/H/3713/IB/003/G	IB	8-2-2019	8-3-2019	Approved	--
The MAH would like to implement the PRAC recommendations	NL/H/3713/IB/004/G	IB	5-3-2019	4-4-2019	Approved	--

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