CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Xylozolin 0.5 mg/ml and 1 mg/ml, nasal spray, solution
Pharmachemie B.V., the Netherlands

xylometazoline hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2237/001-002/DC
Registration number in the Netherlands: RVG 109042-109043

24 September 2012

Pharmacotherapeutic group:	decongestants and other nasal preparations for topical use, sympathomimetics, plain
ATC code:	R01AA07
Route of administration:	nasal
Therapeutic indication:	temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis
Prescription status:	non prescription
Date of first authorisation in NL:	18 September 2012
Concerned Member States:	Decentralised procedure with DK, IE (1 mg/ml only), SE
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Xylozolin 0.5 mg/ml and 1 mg/ml, nasal spray, solution from Pharmachemie B.V. The date of authorisation was on 18 September 2012 in the Netherlands.

The product is indicated for temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis.
A comprehensive description of the indications and posology is given in the SPC.

Xylometazoline is an imidazole derivative with a sympathomimetic effect. In topical use on the nasal mucosa, xylometazoline induces rapid and long-lasting vasoconstrictions as a result of which nasal congestion reduces.
The vasoconstriction induced by xylometazoline is likely transmitted via the pharmaceutical ingredient's direct stimulative effect on the postsynaptic alpha receptors. Rebound symptoms occasionally occurring after long-term use (mucosal swelling and congestion) are likely to be due to the pharmaceutical ingredient's stimulative effect on presynaptic alpha2 receptors and the reducing effect on the release of noradrenaline. With vasoconstrictors, the rebound symptoms normally occur after 2 to 3 weeks of continuous treatment, but xylometazoline has been given to healthy test subjects for up to 6 weeks without mucosal swelling or tachyphylaxis occurring. Xylometazoline is not known to have much effect on adrenergic beta receptors. The use of topical vasoconstrictors in the treatment of sinutitis is based on the pharmaceutical ingredients' congestion-reducing effect that also improves the ventilation of the sinuses and makes it easier to empty them.
Xylometazoline has been observed *in vitro* to reduce the functioning of cilia, but the effect is not permanent.

This decentralised procedure concerns a bibliographical application. The MAH provided information on the comparability of the present product with similar medicinal products available on the (Dutch) market, and with other medicinal products authorised in the EU, namely Otriven® 0.5 mg/ml and 1.0 mg/ml nasal spray and Nasolin®/Rinoxyl® 0.5 mg/ml and 1.0 mg/ml nasal spray, which contain the same active substance in the same concentrations as the proposed nasal sprays. The active substance xylometazoline is well-known and it has been used in the EU in the treatment of nasal congestion that is caused by rhinitis/sinusitis since 1959 (first product authorized in the EU: Otrivin®, emission date 13 May 1988). The use of xylometazoline in the treatment of nasal congestion caused by rhinitis/sinusitis can therefore be considered well established within the EU. In addition, its established medicinal use is supported by the bibliographical literature; therefore the MAH has not performed any additional non-clinical or clinical studies with their product.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC.

This application concerns a bibliographical application based on well-established medicinal use of xylometazoline hydrochloride. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ‘’Medicinal use’’ does not exclusively mean ‘’use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a bibliographical application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for the product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is xylometazoline hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder, which is freely soluble in water, ethanol and 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 new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the additional requirement of the CEP.
Batch analytical data demonstrating compliance with the drug substance specification have been provided by the drug product manufacturer for 3 batches.

Stability of drug substance
The active substance is stable for 4 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Xylozolin 0.5 mg/ml and 1 mg/ml nasal spray contain as active substance either 0.5 or 1 mg/ml xylometazoline hydrochloride, of which 1 dose (0.09 ml) contains either 0.045 or 0.09 micrograms of xylometazoline hydrochloride, respectively.

The nasal spray is packed in brown glass bottles sealed with a PP/PE/Steel spray pump with a nose adapter and a protecting cap (0.5 mg/ml 10 ml; 1.0 mg/ml 10 ml and 1.0 mg/ml 15 ml).

The products are clear, almost colourless solutions with pH 5,5-6 and osmolarity of 250-300 mOsm/kg.

The excipients are: citric acid monohydrate, sodium citrate dihydrate, glycerol 85%, water for injections.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients used are well known. The choices of the packaging and manufacturing process are justified. The main development studies performed were in line with the guideline on pharmaceutical quality of inhalation and nasal products. No overages are used. The manufacture and filling under strictly aseptic conditions can be regarded as an additional measure. All parts coming into contact with the product are sterilized before the manufacture. The solution is sterile-filtered and filled in sterilized primary packaging under clean room conditions. No bioequivalence studies were performed as the application is a well-established use application. The pharmaceutical development has been adequately performed.

Manufacturing process

Xylometazoline nasal spray is manufactured under nitrogen and sterile filtered under nitrogen pressure. The glass bottles are sterilized by a hot-air sterilization tunnel process and the spray pumps are sterilized by ethylene oxide. The filling machine and the sealing machine are located in a sterile room, conditions correspond to class 100. The solution is filled into the primary packaging under Laminar Flow. The manufacturing process has been adequately validated.

Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

Microbiological attributes

The suitability and efficacy of the multidose container system for a nasal preparation without preservatives is discussed. The results of the investigations prove that the drug product complies with the requirements of the Ph.Eur. Data for the microbiological in use stability showed no microbial contamination after 12 months of simulated use.

Quality control of drug product

The product specification includes tests for description, identity, pH, osmolality, density, colouration, uniformity of dose, mean delivered dose, number of spraying impacts, assay, related substances and sterility. The release and shelf life limits are identical with the exception of related substances. Based on the stability data provided, this difference between release and shelf life limits is acceptable.
Based on batch analysis data and stability data the specification is acceptable; the limits for number of spraying impacts has been tightened. Limits for droplet size distribution have been included. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three production-scale batches of each strength, demonstrating compliance with the release specification..

Stability of drug product

Stability data on the product has been provided for the following batches:

- 0.5 mg/ml 10 ml: three full-scale batches stored at 25°C/60% RH (36 months), 30°/70% RH (12 months) and 40°C/75% RH (6 months).
- 1.0 mg/ml 10 ml: three pilot-scale batches stored at 25°C/60% RH (48 months), 30°/70% RH (48 months) and 40°C/75% RH (12 months) and three full-scale batches stored at 25°C/60% RH (36 months), 30°/70% RH (12 months) and 40°C/75% RH (6 months).
- 1.0 mg/ml 15 ml: three full-scale batches stored at 25°C/60% RH (36 months), 30°/70% RH (12 months) and 40°C/75% RH (6 months).

The batches were stored in brown glass bottles (10 or 20 ml) with 3K Pumps 0.09 ml.
One out-of-specification result was observed for mean delivered dose at accelerated conditions. Given the results of this batch at intermediate conditions this result is considered an outlier. Increases were observed in one impurity in both strengths, in both container sizes and at all conditions. However, all results for this impurity remained within specification. All other parameters tested remained relatively stable and within specifications. Based on the stability data provided, the proposed shelf-life of 36 months without special storage conditions is justified.

In-use stability

The in-use stability data provided showed a slight increase one impurity. However, results remained with the specifications. All other parameters tested remained relatively stable and within specifications The in-use stability data adequately demonstrate that the product remains stable for 12 months following first opening of the container (without special storage conditions).

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.2 Non-clinical aspects

This active substance has been available on the European market for many years. Pharmacodynamic, pharmacokinetic and toxicological properties of xylometazoline are well known. Xylometazoline is a widely used, well-known active substance. Xylometazoline is a topical sympathomimetic vasoconstrictor. It is structurally and pharmacologically related to other imidazoline derivatives such as naphazoline, oxymetazoline, and tetrahydrozoline. Xylometazoline is a direct-acting α-adrenoceptor agonist with affinity to both, α1- and α2-adrenoceptors. Current evidence indicates that within the nasal mucosa xylometazoline stimulates α2-adrenoceptors located on postcapillary venules and α1-adrenoceptors which are largely concentrated on precapillary arterioles.
A non-clinical overview has been submitted referring to 46 publications up to year 2010. The non-clinical overview is adequate. It demonstrates that xylometazoline has a well established use with an acceptable level of safety on the basis of published information on the pharmacological and toxicological properties of the product. An overview based on literature review is, thus, appropriate. No further studies are required and the applicant provides none.

Environmental risk assessment
An Environmental risk assessment has been submitted. The environmental impact of xylometazoline has been assessed in accordance to the Guideline on the environmental risk assessment of medicinal products for human use, EMEA/CHMP/SWP/4447/00 corr 1. The predicted environmental concentration in surface water was below the action limit (10 ng/L); further assessment is therefore not deemed necessary. To complete the PBT assessment, the MAH has committed to submit an experimentally determined value for log $K_{ow.}$ If the K_{oc} will be above 4, the slow stirring method (oecd 123) will be conducted to estimate the K_{ow}. The study report will be submitted upon availability.

II.3 Clinical aspects

Xylometazoline is a well-known active substance with established efficacy and tolerability. The Clinical Overview submitted contains 60 detailed references to published literature (up to 2010) as well as data from other clinical reports.

Pharmacokinetics
There are no data available on the distribution, metabolism of excretion of xylometazoline in humans. But in humans, xylometazoline is systemically available to some extend based on reported side effects.

Clinical efficacy
Short-term use of xylometazoline in the symptomatic relief/alleviation of nasal congestion is well-established. Xylometazoline frequently induces a rapid decongestant effect, with instantly diminished nasal airflow resistance and an increase of air flow, inspiratory as well as expiratory. To date there are few controlled trials comparing xylometazoline with other imidazoline derivatives. It appears that, except for a longer duration of action than with other similar agents, xylometazoline offers no particular advantage in efficacy or safety when compared with other imidazoline decongestants.

Clinical safety

Intranasal use of xylometazoline has been associated with a number of local side effects: burning sensation, stinging, sneezing and also dryness of the nasal mucosa. Long-term use can cause nasal stuffiness (rhinitis medicamentosa) and tolerance to the effect.

Depression of ciliary function in nasal mucosa has been observed after intranasal use of decongestants. In case of xylometazoline, the cilia-inhibitory action is not due to the active ingredient, but is more likely caused by benzalkonium chloride, present in some preparation as the innovator Otrivin®. Xylometazoline nasal spray does not contain benzalkonium chloride.

After intranasal administration, xylometazoline seldom produces significant systemic adverse effects. Palpitations have been infrequently observed. After overdose, significant cardiovascular effects may occur, including hypertension and arrhythmias. Nausea and vomiting have rarely been reported.

CNS effects are mild, infrequent, and rarely occur after therapeutic intranasal doses. However, headache, insomnia, dizziness, weakness, or tremors may be observed in patients who are sensitive to small doses of catecholamines or after overdoses. Xylometazoline is capable of depressing the CNS, with drowsiness and profound CNS depression occurring after excessive doses in children.

Risk of interaction between intranasal xylometazoline and other medicinal products is low. If significant systemic absorption of nasal xylometazoline occurs, concurrent use of monoamine oxidase (MAO) inhibitors or tricyclic antidepressants may potentiate the vasopressive effect of xylometazoline.

Risk management plan

Xylometazoline has been used for many years. The safety profile of xylometazoline can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with those accepted for other xylometazoline products approved through recent DCPs.

Readability test

The package leaflet 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, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Xylozolin 0.5 mg/ml and 1 mg/ml, nasal spray, solution have a proven chemical-pharmaceutical quality. The MAH has submitted a dossier compliant with a bibliographical application based on well-established medicinal use of xylometazoline hydrochloride. The products are similar to the other medicinal products authorised in the EU, namely Otrivin 0.05% and 0.1% nasal spray and Nasolin®/Rinoxyl® 0.5 mg/ml and 1.0 mg/ml nasal spray, which contain the same active substance in the same concentrations as the proposed nasal sprays. The MAH submitted a literature review on pre-clincal and clinical data supporting the efficacy, safety and wide use of xylometazoline.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other xylometazoline containing products.

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 well-established use has been demonstrated for Xylozolin 0.5 mg/ml and 1 mg/ml, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 3 January 2012. Xylozolin 0.5 mg/ml and 1 mg/ml, nasal spray, solution were authorised in the Netherlands on 18 September 2012.

The date for the first renewal will be: July 2014.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to store further production batches (one batch of each strength and each container size) in upright and inverted orientation. In case of significant changes in results reporting will follow promptly.
- The MAH committed to subject one batch of each strength and each container size towards the end of its shelf-life to in-use stability testing.

Non-clinical aspects

- The MAH committed to submit an experimentally determined value for log K_{ow}.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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