CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nasadur 1 mg/ml and 0.5 mg/ml nasal spray, solution
Premier Research GmbH, Germany

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/1996/001-002/DC
Registration number in the Netherlands: RVG 107407 and 107408

22 November 2012

Pharmacotherapeutic group:	decongestants and other nasal preparations for topical use, sympathomimetics, plain
ATC code:	R01AA07
Route of administration:	nasal
Therapeutic indication:	symptomatic treatment of nasal congestion in children 2-10 years (0.5 mg/ml) and in patients aged 10 years and over (1 mg/ml)
Prescription status:	non prescription
Date of authorisation in NL:	4 September 2012
Concerned Member States:	Decentralised procedure with DE
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 Nasadur 1 mg/ml and 0.5 mg/ml nasal spray, solution, from Premier Research GmbH. The date of authorisation was on 4 September 2012 in the Netherlands.

The product is indicated for symptomatic treatment of nasal congestion. The 1 mg/ml nasal spray may be used in adults and in children aged 10 years and over, and the 0.5 mg/ml nasal spray may be used in children from 2 to 10 years.

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

Xylometazoline is an imidazoline derivative with sympathomimetic effects. In topical use on the nasal mucosa, xylometazoline induces rapid and long-lasting vasoconstrictions as a result of which nasal congestion reduces. Patients with sinusitis or tubular catarrh could be treated with this medicinal product if any other complications (e.g. bacterial sinusitis) can be excluded.
Symptoms of a rebound effect which sometimes occur with long-term use (mucous membrane swelling and congestion) are probably caused by the stimulating effects of the constituents on pre-synaptic alpha2 receptors and the suppressing effects on noradrenalin release. With vasoconstrictors, rebound-effect symptoms usually occur after 2 to 3 weeks of continuous treatment. However, xylometazoline has been administered in tests to healthy individuals for a period of 6 weeks without occurrence of mucous membrane swelling or tachyphylaxis. Xylometazoline is not known to have much effect on adrenergic beta receptors. The use of topical vasoconstrictors in the treatment of sinusitis 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 application concerns a bibliographical application based on well-established medicinal use of xylometazoline hydrochloride. This active substance has been used in the EU in the treatment of nasal congestion caused by rhinitis/sinusitis since 1959 (first product authorised in the EU: Otriven, harmonized birth date 13 May 1988) and its well established medicinal use is supported by bibliographical literature. 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.

In this decentralised procedure, well-established use is substantiated based on essential similarity with Otriven 0.05% and 0.1% nasal spray, and Nasolin/Rinoxyl 0.05% and 0.1% nasal spray, which contain the same active substance in the same concentrations as the proposed nasal sprays. Nasolin/Rinoxyl were authorised via a bibliographic application in 2009 (FI/H/0731/001-002/MR) and the wording of the proposed SmPCs is based on that of the respective Nasolin/Rinoxyl product (Rinoxyl SmPC, 2009). The qualitative composition of the proposed product is identical to that of Snup Schnupfenspray 0.05%/0.1% nasal spray solution authorised for STADA GmbH in Germany since 1998 and Mar Rhino 0.05% / 0.1% nasal spray authorized for STADA Arzneimittel AG in Czech Republic since 2006. Otrivin nasal drops and Otrivin nasal spray 1 mg/ml were first registered in the Netherlands by Novartis consumer health in 1978. The NL Otrivin marketing authorisations have been transferred to Sandoz B.V. and the products are currently registered as Xylometazoline HCl Sandoz 0.5 and 1.0 mg/ml nasal drops (NL License RVG

03940-03941) and Xylometazoline HCl Sandoz 0.5 and 1.0 mg/ml nasal spray (NL License RVG 13032 and 05370).

Scientific advices were given by the following Member States: Czech Republic and the Netherlands prior to dossier submission. The topics discussed related to the quality part of the dossier and guidance with respect to the possibility of submitting a well-established use application.

No paediatric development programme has been submitted.

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.*). Xylometazoline hydrochloride is a white to almost white, crystalline powder. The drug substance is freely soluble in water. Xylometazoline is susceptible to hydrolysis, the course of which is influenced by pH en temperature. Xylometazoline hydrochloride is fairly stable in acid or neutral media (pH 5-7), whereas in alkaline media the rate of hydrolysis is considerably increased. The substance does not exhibit chirality.

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

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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance
The active substance is stable for 4 years when stored under the proposed 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
Nasadur 1 mg/ml and 0.5 mg/ml nasal spray contain as active substance either 1 or 0.5 mg/ml xylometazoline hydrochloride, of which 1 dose (= 90 microlitres) contains either 90 or 45 micrograms of xylometazoline hydrochloride, respectively. The formulation contains no preservative.

The nasal spray is packed in 10 ml multidose HDPE bottles with a PP/PE/Steel spray pump attached to the bottle neck with a plastic cover. The filling volume is 11.5 g per bottle. The products are clear and colourless solutions with pH 5.5-6.5 and osmolality of 0.260-0.320 osmol/kg.

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

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It was decided to develop a preservative free sterile nasal spray to avoid known side effects caused by typical preservatives used in preparations for nasal application (e.g. benzalkonium chloride).
The main development studies performed were comparative studies with similar products, optimization of the formulation and testing of a suitable container closure system. The choices of the packaging and manufacturing process are justified. The development of the manufacturing process was described in sufficient detail. The use of aseptic processing and sterilizing by filtration is justified and the suitability and the validity of the used sterilizing filter.
The use of sea water is in principle acceptable as pharmaceutical excipient; it can be seen as a specified quality of water. Besides, it is used in nasal sprays from the same company without xylometazoline and it can therefore be assumed that this excipient is well tolerated and safe.
Comparative results for uniformity of mass (by Ph.Eur. method) between two batches of the test product (both strengths) and two batches of the preservative free Otrivin® comparator product were performed, showing comparable results. The declared delivered dose of the comparator product is 90 µl per spray. Droplet size distribution was also demonstrated to be in accordance with Otrivin. No bioequivalence studies were performed as the application is a well-established use application. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of bulk manufacture, sterile filtration and filling, and is performed under aseptic conditions. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches per strength.

Excipients
Except for sea water, the excipients comply with Ph.Eur. requirements. These specifications are acceptable. An in-house specification for sea water is provided, which is acceptable.

Quality control of drug product
The product specification includes tests for appearance, pH, osmolality, identification, assay, related substances, sterility, droplet size distribution, uniformity of dosage units, mass of dosage units and number of actuations per container. Except for related substances, the release and shelf-life limits are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scale batches per strength, demonstrating compliance with the release specification.

Microbiological attributes
The test for sterility following Ph.Eur 2.6.1 is carried out.

Container closure system

The drug product is packed in HDPE bottles with spray pump. The compatibility of the selected materials was confirmed by the results of stability testing. A preservative-free spray pump was chosen to enable the exclusion of a preservative from the multi-dose formulation. The mechanism of actuation of the chosen system is described. In the chosen pump system for nasal products the valve re-closes immediately and simultaneously with delivering the defined amount of product. The pressure in the bottle is equalized by introducing ambient air via an antibacterial filter matrix.

Stability of drug product
Stability data on the product have been provided on three full scale batches per strength stored at 25°C/65% RH (up to 24 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 HDPE bottles with a spray pump. An increase of impurities is seen mainly at accelerated conditions. No significant changes are seen for the other parameters and all results are within the specified limits. Forced degradation (photostability) studies performed as part of the validation of the analytical methods for assay and related substances show no degradation after UV treatment for 24 hours (according to ICH requirements). The proposed shelf-life of 30 months without any special storage requirements is justified. Stability data has been provided, demonstrating that the product remains stable for three months following first opening of the container.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of xylometazoline hydrochloride are well known. As xylometazoline hydrochloride is a widely used, well-known active substance, no further studies are required. An overview based on literature review is, thus, appropriate. The MAH submitted a non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology. This overview is adequate.

Environmental risk assessment
In the environmental risk assessment the $PEC_{surfacewater}$ does not exceed the trigger value, and therefore no phase II studies are required. Besides the phase I and II studies and irrespective of their outcome, xylometazoline should be subjected to screening for persistence, bioaccumulation and toxicity, as this is required for all marketing authorization applications. Experimental data are the basis of the PBT screening. The log K_{ow} should be determined experimentally. The MAH committed to perform experimental studies to determine the log K_{ow} and submit the results to the authorities as soon as they are available.

II.3 Clinical aspects

As this is an article 10a "well-established use" application for a medicinal product containing an active substance which has been used in the EU in the treatment of nasal congestion caused by rhinitis/sinusitis since 1959, no new clinical trial reports have been submitted. Assessment of clinical data is based exclusively on literature overview.

Clinical efficacy
The active ingredient xylometazoline hydrochloride is intended to act without systemic absorption. Therefore the product belongs to the category of locally acting products. Consequently, determination of bioequivalence based on systemic measurements is not applicable (Note for guidance on the investigation of bioavailability and bioequivalence, CPMP/EWP/QWP/1401/98).

The MAH has not carried out biopharmaceutical or clinical efficacy studies with this product (Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents, CPMP/EWP/239/95).

Short-term use of xylometazoline in the alleviation of nasal congestion is well-established.
Xylometazoline possesses a rapid decongestant effect, with a decrease in nasal airflow resistance and increase of inspiratory flow. 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 advantage in efficacy or safety over other imidazoline decongestants.

Clinical safety
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).

Depression of ciliary function in nasal mucosa has been observed after intranasal use of decongestants. In case of xylometazoline, the cilioinhibitory action is not due to the active ingredient, but is more likely caused by preservative agents, such as benzalkonium chloride. Nasadur nasal spray does not contain benzalkonium chloride or other preservatives.

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.

Central nervous system (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 pressor 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 that accepted for other xylometazoline products.

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 was performed with the package leaflet for the 0.5 mg/ml nasal spray. 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 readability test has been sufficiently performed.
For the PIL of the 1 mg/ml strength a bridging statement was provided. The comparison of both leaflets showed only minor differences in content and layout because of the different strengths, which were

evaluated as not relevant; most key messages for the patients are similar. Therefore, no separate user testing of Nasadur 1 mg/ml nasal spray, solution Leaflet was necessary.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nasadur 1 mg/ml and 0.5 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 MAH claimed essential similarity of Nasadur 1 mg/ml and 0.5 mg/ml nasal spray, solution to other medicinal products authorised in the EU, namely Otriven 0.05% and 0.1% nasal spray and Nasolin/Rinoxyl 0.05% and 0.1% nasal spray, which contain the same active substance in the same concentrations as the proposed nasal sprays.

The active substance has been used in the EU in the treatment of nasal congestion caused by rhinitis/sinusitis since 1959; no new clinical trial reports have been submitted. Assessment of non-clinical and clinical data is based exclusively on literature overview.

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 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 essential similarity has been demonstrated for Nasadur 1 mg/ml and 0.5 mg/ml nasal spray, solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 September 2011. Nasadur 1 mg/ml and 0.5 mg/ml nasal spray, solution were authorised in the Netherlands on 4 September 2012.

The date for the first renewal will be: 20 September 2016.

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

<u>Quality - medicinal product</u>

- The MAH committed to continue the ongoing stability studies. The results at least up to the proposed shelf-life of 30 months will be provided as soon as available.
- The MAH committed to add top-down samples to the stability studies as requested. The results of these studies will be available on request or submitted whenever the results clearly deviate from the currently available stability data or out-of-specifications occur.
- The MAH committed to repeat the in-use stability study at the end of shelf-life of the tested batches. The results of these studies will be available on request or submitted whenever the results clearly deviate from the currently available in-use stability data or out-of-specifications occur.

<u>Non Clinical aspects</u>

- The MAH committed to perform a study to experimentally determine log K_{ow}. A variation will be submitted for assessment of the results.

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
K_{ow}	Octanol-Water Partition Coefficient
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
$PEC_{surfacewater}$	Predicted Environmental Concentration (surfacewater)
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