

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Xylometazoline HCl 0.5 mg/ml and 1 mg/ml nasal drops
Xylometazoline HCl 1 mg/ml nasal spray
Basic Pharma Manufacturing bv, 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/1763/001-002-004/MR
Registration number in the Netherlands: RVG 32865, 17074, 32867**

2 July 2010

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:	nasal drops 1 mg/ml: 29 June 1995 nasal drops 0.5 mg/ml + nasal spray 1 mg/ml: 18 December 2006
Concerned Member States:	Mutual recognition procedure with BE, DE, PL (all products); nasal spray only - DK, EE, FI, LT, LV, NO, SE
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

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 Xylometazoline HCl 0.5 mg/ml and 1 mg/ml nasal drops, and Xylometazoline HCl 1 mg/ml nasal spray, from Basic Pharma Manufacturing bv. The date of authorisation for Xylometazoline 1 mg/ml nasal drops was on 29 June 1995 in the Netherlands. Xylometazoline HCl 0.5 mg/ml nasal drops and 1 mg/ml nasal spray were authorised in the Netherlands on 18 December 2006. The MAH withdrew the application for Xylometazoline HCl 0.5 mg/ml nasal spray in all Member States (see II.3 Clinical aspects).

The products are 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 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 mutual recognition procedure concerns a hybrid application claiming essential similarity with the innovator products Otrivin neusverkoudheid Xylometazoline 0.5 mg/ml and 1 mg/ml Classic, nose drops (NL License RVG 03940-03941) and Otrivin neusverkoudheid Xylometazoline 1 mg/ml Classic, nose spray (NL RVG 13032). Otrivin nasal drops and Otrivin nasal spray 1 mg/ml were first registered in the Netherlands by Novartis consumer health in 1978. In addition, reference is made to Otrivin authorisations in the individual member states (reference product). The NL Otrivin marketing authorisations have been transferred to Sandoz B.V., and the products are currently registered as Xylometazoline HCl Sandoz nasal drops and Xylometazoline HCl Sandoz nasal spray.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. In accordance with the *Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products containing Known Constituents* (CPMP/EWP/239/95), the MAH has demonstrated essential similarity through *in vitro* comparison of its Xylometazoline HCl formulation with the innovator product. The current products can be used instead of their reference products.

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 hybrid 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 these product types 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.*). It is a white or almost white crystalline powder, which is freely soluble in ethanol and soluble in water. The substance does not exhibit chirality.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

A narrative description of the synthesis is given. The manufacturing process is divided in two stages. Adequate requirements have been laid down for the starting materials, intermediates, solvents and reagents. The purified Xylometazoline HCl is sufficiently characterized.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. with additional requirements for residual solvents. 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 3 full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for 3 full-scale batches stored at 30°/70% RH (48 months) and 40°C/75% RH (6 months). No trends or changes have been observed during the stability study. Therefore, the proposed shelf-life of 48 months and retest period of 24 months could be granted.

* *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

Xylometazoline HCl 0.5 mg/ml nasal drops contains as active substance per single dose (22 mg) 10.9 microgram xylometazoline hydrochloride. The nasal drops are packed in brown glass bottles (hydrolytic type III, content 10 ml) with a glass, transparent dropper tube which is provided with a thermoplastic gummi balloon, a polypropylene cap and a polyethylene ring.

Xylometazoline HCl 1 mg/ml nasal drops contains as active substance per single dose (22 mg) 21.8 microgram xylometazoline hydrochloride. The nasal drops are packed in brown glass bottles (hydrolytic type III, content 10 ml) with a transparent glass pipette which is provided with a thermoplastic gummi balloon, a polypropylene screw cap and a polyethylene ring.

Xylometazoline HCl 1 mg/ml nasal spray contains as active substance per single dose (140 microliter) 140 microgram xylometazoline hydrochloride. The nasal spray is packed in brown glass bottles (hydrolytic type III) with a dosage mechanism of polyethylene and polypropylene cap, content 10 ml.

The products are clear and colourless solutions.

The excipients are: benzalkonium chloride, disodium edetate, sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, sodium chloride, purified water.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The qualitative composition is in line with the innovator products. Comparative drop sizes and spray volumes with the innovator products have been provided, demonstrating similarity. Moreover, the pH, density and osmolarity are similar to those of the innovator products.

Since the formulation contains an antimicrobial preservative it was necessary to assess the antimicrobial efficacy of the preservative in the drug product according to the Ph.Eur. test during the development of the formulation. From this test it was concluded that benzalkonium chloride in the concentration applied in the formulation (0.01% w/v) obtained adequate preservative properties in the nasal solution. The pharmaceutical development of the product has been adequately performed.

The MAH has provided a comparative drop size study between the xylometazoline HCl nasal drops 0.5 and 1 mg/ml and several xylometazoline products on the Dutch market, including the innovator product. The results of the comparative study show that the average drop size weight of the Basic Pharma product is 22 mg, while the other products have a average drop size weight of 20.3 mg (innovator) and 22.4 mg (Kinderneusdruppels RVG 21871=55140) and 23.6 mg (Neusdruppels RVG 21873=55141). The drop sizes of the different products are considered to be similar.

Spray-volume of the nasal sprays at issue and of the innovator product has been compared. It is stated that deviation of the mean spray-volume was found acceptable in view of the Ph.Eur specification for uniformity of spray-volume for nasal spray preparations.

Manufacturing process

The preparation of the solutions is a straight-forward process. The solution is filtered prior to filling it out in bottles. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 pilot-scale batches at an old production site. For a new production site, 2 subsequent production-scale batches of have been validated according to the validation protocol submitted.

Control of excipients

The excipients comply with their Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, colour, clarity, identity (xylometazoline HCl and disodium edetate), assay (xylometazoline HCl, disodium edetate and benzalkonium chloride), pH, uniformity of content of bottles, related substances and microbiological purity. The release and shelf-life requirements are identical. The requirements laid down for the drug products are adequate.

The analytical methods have been adequately described and validated. Batch analytical data from the production site have been provided on 3 pilot-scale batches, demonstrating compliance with the release specification.

The MAH committed to provide a justification for the specified range of 35-95 µm for the d50 of the droplet size distribution. Also, a commitment was made to compare and assess the droplet size distribution of the generic nasal spray to the Dutch innovator product, with sufficient batches to take batch variability into account.

Stability of drug product

Stability data on the products has been provided on 3 pilot scaled batches of each strength stored at 25°C/60% RH (36 months) and 40°/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in amber brown 10 ml class III glass bottles. No increase in impurity levels is observed. No out-of-specifications were observed. The proposed shelf-life of 3 years and the storage condition *Store below 25°C* were therefore granted.

Stability data has been provided demonstrating that the product remains stable for 1 month following first opening of the bottle. The prescribed use of the formulation was simulated for 4 weeks. The results showed no trends in the tested parameters.

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 product is a generic formulation of Otrivin, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of xylometazoline released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Xylometazoline is a well-known active substance with established efficacy and tolerability.

Xylometazoline HCl 0.5 mg/ml and 1 mg/ml nasal drops, and Xylometazoline HCl 1 mg/ml nasal spray are locally applied, locally acting medicinal products and therefore fulfil the exemption mentioned in the Note for Guidance on bioequivalence, which states that an exemption for bioequivalence study can be granted if the product is locally applied containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Xylometazoline HCl 0.5 mg/ml and 1 mg/ml nasal drops, and Xylometazoline HCl 1 mg/ml nasal spray is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current products can be used instead of their reference products.

Risk management plan

Xylometazoline was first approved in 1988, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of xylometazoline can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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.

Withdrawal of 0.5 mg/ml nasal spray

An issue was raised regarding the spray pump volume of the 0.5 mg/ml nasal spray product, which is bigger than the originator's in several countries. The MAH chose to withdraw Xylometazoline HCl 0.5 mg/ml nasal spray prior to day 90 of the procedure, i.e. on 27 November 2009. The evaluation of the 0.5 mg/ml nasal drops was mutually recognised and adopted on finalisation of the MRP.

Discussion on posology

The MAH adopted the posology of the Dutch innovator for the 1 mg/ml products: 2-3 drops in each nostril up to 4-6 times a day which is 8-18 drops daily. In some other member states, the recommended posology/daily dose for the innovator products is lower (for example, 1-2 drops per nostril up to 3-4 times a day; this is slightly different in several CMSs). In the Netherlands and some of the participating member states, xylometazoline nasal drops and spray are indicated for patients > 6 years. In some other countries, the limit is > 10 years.

With respect to proposed dose recommendation as well as the proposed age limit, more detailed evidence concerning the efficacy and safety of the proposed total daily dose was required by some

CMSs. During the procedure, these issues could not be resolved. Therefore, a CMD(h) referral was initiated on 7 December 2009.

CMD(h) referral

During the CMD(h) referral the MAH addressed the concerns regarding age and posology. A discussion was held on 16 February 2010, resulting in a proposal to lower the frequency of dosing to 3 times a day and to raise the age limit from 6 years to 10 years, i.e:

Nasal drops 1 mg/ml

Adults and children >10 years of age: 3 times a day, 2-3 drops in each nostril

Nasal spray 1 mg/ml

Adults and children >10 years of age: 3 times a day, 1 spray in each nostril

Agreement could be reached on this proposal, and the CMD(h) referral ended positively on 25 February 2010.

Product information

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 conducted with a total of 20 participants. Sixteen questions were asked. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question met the criterion of 81% correct answers. A few points were considered after feedback from the participants. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Xylometazoline HCl 0.5 mg/ml and 1 mg/ml nasal drops, and Xylometazoline HCl 1 mg/ml nasal spray have a proven chemical-pharmaceutical quality and are generic forms of Otrivin 0.5 mg/ml and 1 mg/ml Classic nasal drops, and Otrivin 1 mg/ml Classic nasal spray. Otrivin is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are locally applied, locally acting medicinal products, no bioequivalence study is deemed necessary.

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. Xylometazoline 1 mg/ml nasal drops were authorised in the Netherlands on 29 June 1995, and Xylometazoline 0.5 mg/ml nasal drops and 1 mg/ml nasal spray on 18 December 2006.

The 1 mg/ml nasal drops and spray were referred to the CMD(h) as there are issues identified by some member states concerning the indicated range of age of the target population as well as the posology. The Dutch innovator is indicated for patients > 6 years, while the age limit is > 10 years in a couple of CMSs. In addition, the recommended dose of the Dutch innovator is higher compared to that of all of the other participating CMSs.

In the CMD(h) discussion, agreement between member states was reached to lower the frequency of dosing to 3 times a day and to raise the age limit from 6 years to 10 years. The CMD(h) procedure was finished on 25 February 2010. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Xylometazoline HCl 0.5 mg/ml and 1 mg/ml nasal drops, and Xylometazoline HCl 1 mg/ml nasal spray with the reference product, and have therefore granted a marketing authorisation.

A European harmonised birth date has been allocated (13 May 1988) and subsequently the first data lock point for xylometazoline is May 2011. The first PSUR will cover the period from February 2010 to May 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 November 2014

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

Quality - medicinal product nasal spray 1 mg/ml

- The MAH committed to provide a justification for the specified range of 35-95 µm for the d50 of the droplet size distribution.
- The MAH committed to compare and assess the droplet size distribution of the generic nasal spray to the Dutch innovator product, with sufficient batches to take batch variability into account.

Pharmacovigilance system

- The MAH committed to submit an updated version of the Pharmacovigilance system.

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 _{1/2}	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