CBG MEB

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

# Xylometazoline HCl/Dexpanthenol 0.5/50 mg/ml and 1.0/50 mg/ml ratiopharm, nasal spray, solution ratiopharm Nederland B.V., the Netherlands

## xylometazoline hydrochloride/dexpanthenol

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/2457/001-002/DC**
**EU-procedure number: NL/H/2537/001-002/DC**
**Registration number in the Netherlands: not applicable**

**26 June 2013**

| | |
|---|---|
| Pharmacotherapeutic group: | sympathomimetics, combinations excl. corticosteroids |
| ATC code: | R01AB06 |
| Route of administration: | nasal |
| Sought indication: | temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis; supportive treatment allowing better tolerability and shorter treatment than xylometazoline alone |
| Prescription status: | non prescription |
| Date of authorisation in NL: | Not applicable, application withdrawn |
| Concerned Member States: | Decentralised procedure with AT, BE, BG, CZ, DE, DK, FI, HU, IE, LU, MT, PL, RO, SI, SK (2457); DE (2537) |
| 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 data and the applicant's responses to the questions raised by RMS and CMSs on quality, safety and efficacy, the member states consider that the application for

Xylometazoline HCl/Dexpanthenol 0.5/50 mg/ml ratiopharm, nasal spray, solution and
Xylometazoline HCl/Dexpanthenol 1.0/50 mg/ml ratiopharm, nasal spray, solution

in the proposed indication:

- *temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis and as supportive treatment allowing better tolerability and shorter treatment than xylometazoline alone*

for adults as well as for children 10 years of age and older (1 mg/ml xylometazoline) and children between 2 and 10 years of age (0.5 mg/ml xylometazoline)

is **not approvable** since a potential serious risk to public health (PSRPH) has been identified, which precludes a recommendation for marketing authorisation.

The initial indication applied for was *temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis and as supportive treatment in the healing of skin and mucosa*. This proposed indication was also rejected. The applicant changed the wording of the indication during the procedure.

The PSRPH pertains that the provided literature is considered insufficient to support the new claimed indication based on well-established use.

Considering this assessment, the applicant decided to withdraw the application before finalisation of the decentralised procedure. Therefore no marketing authorisation has been granted.

Xylometazoline acts as a nasal decongestant of sympathomimetic class. Xylometazoline remains one of the most frequently prescribed nasal decongestants.
Dexpanthenol acts as a nasal soothing ointment. Dexpanthenol is the alcohol analogue of a precursor to pantothenic acid. The vitamin pantothenic acid has no accepted therapeutic uses in human medicine, though it has been given orally as a nutritional supplement.
According to the applicant, the rationale of the combination is that it provides a shorter treatment period and allows a better tolerability than xylometazoline alone.

This application concerns a bibliographical application based on well-established medicinal use of the xylometazoline/dexpanthenol combination, in accordance with article 10a of Directive 2001/83/EC. 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.

Xylometazoline fulfils the criterion of being used clinically as a nasal decongestant for longer than a decade; it has been used for half a century since its approval, e.g. by the US Food and Drug Administration (FDA) in 1959. Dexpanthenol fulfils the criterion of being used clinically as a topical treatment for nasal mucosal sores for longer than a decade. It is not known if it is being used "as supportive treatment allowing better tolerability and shorter treatment than xylometazoline alone".
Dexpanthenol itself has been used for more than half a century for topical and systemic clinical use since its approval, e.g. by the US Food and Drug Administration (FDA), in 1948.

Combination therapy with a nasal decongestant (xylometazoline) and a nasal soothing ointment or solution (5% dexpanthenol) has been possible for more than two decades "for the temporary symptomatic

treatment of nasal congestion due to rhinitis or sinusitis as supportive treatment in the healing of skin and mucosa" (Bundesgesundheitsamt 1994) and nasal soothing ointment (Bundesgesundheitsamt 1993), respectively. The combination nasal spray of this application facilitates such treatment.

Pursuant to Directive 2003/63/EC Annex Part II(1)(a), a nasal spray containing both xylometazoline hydrochloride and dexpanthenol fulfils the criterion of being used clinically as a nasal decongestant that improves mucosal sores for longer than a decade. The originator product Nasic® (with either 0.1% or 0.05% xylometazoline hydrochloride and 5% dexpanthenol) received approval for this indication in June 1999 in Germany and additionally in Austria, Bulgaria, Switzerland, Czech Republic, Hungary and Rumania. Xylometazoline hydrochloride and dexpanthenol and its use have been widely documented in literature reflecting a scientific interest in these substances.

The use of xylometazoline in the treatment of nasal congestion in rhinitis associated with the common cold, allergic rhinitis, and sinusitis is considered well-established and is adequately described in the clinical overview.

No literature has been provided demonstrating the use of dexpanthenol monotherapy as a well-established therapy in the treatment of nasal congestion due to rhinitis and sinusitis, neither as monotherapy, nor as step-up therapy due to insufficient response to xylometazoline, nor as additional therapy to reduce the side effects of xylometazoline (nasal dryness). The medical need for alleviating these side effects has not been substantiated.

The provided literature regarding the use of the combination for relieve of nasal congestion is limited. The applicant provided two clinical studies to support the rationale for use of dexpanthenol in the xylometazoline/dexpanthenol combination in the claimed indication 'and as supportive treatment allowing better tolerability and shorter treatment with xylometazoline alone'. Both studies were performed in adults using the 1.0/50 mg/ml spray. In one study (n=151) the effect of the combination was compared with xylometazoline alone in acute non-allergic rhinitis. In the other study, the effect of the xylometazoline/dexpanthenol was compared with xylometazoline for the treatment of rhinitis after nasal surgery (n=61). This is considered a rare cause of rhinitis and of limited value to support the acclaimed indication. It is therefore regarded as a supportive study.

No literature regarding the use of the combination of xylometazoline/dexpanthenol in allergic rhinitis, sinusitis, or in children and adolescents has been provided. This means that efficacy and safety data for a large part of proposed target populations are missing. This is a basic requirement of the documentation in patients groups with a variety of symptoms and disease conditions (CPMP EWP/2330/99). No studies in children using the lower dose combination 0.5/50 mg/mL spray combination were provided either.

The adverse events of the combination product are sparsely described, which makes it not feasible to compare the adverse events rates. No post marketing safety results have been provided.

No scientific advice has been given to the applicant with respect to these products and 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 this 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 substances are xylometazoline hydrochloride and dexpanthenol; both are established active substances described in the European Pharmacopoeia (Ph.Eur.*). Xylometazoline hydrochloride is a white or almost white, crystalline powder, which is freely soluble in water. Dexpanthenol is a colourless or slightly yellowish, viscous liquid, or a white or almost white, crystalline powder, which is very soluble in water.

The CEP procedure is used for both active substances. 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 European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specifications are in line with the Ph.Eur. and the CEPs. The specifications are 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 batches of each drug substance.

Stability of drug substance
Stability data on the active substance dexpanthenol have been provided for three full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). A significant increase in impurities is seen at accelerated storage conditions. At long-term conditions all results remain within the specified limits. The proposed retest period of 36 months with storage condition “Store below 25°C” is justified.
Xylometazoline hydrochloride 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
Xylometazoline HCl/Dexpanthenol 0.5/50 mg/ml and 1.0/50 mg/ml ratiopharm are clear, almost colourless solutions with pH 5.2-6.2 and osmolality of 380-430 mOsmol/kg.

The nasal spray is packed in amber coloured beaded rim glass bottles containing 10 ml solution sealed with a PP/PE/Steel spray pump with a nose adapter and a protecting cap.

The excipients are: disodium hydrogen phosphate heptahydrate, potassium dihydrogen phosphate, water for injections.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies regarded the characterization of the originator products, optimization of the excipient concentrations and several development studies with regard to the nasal spray pump. The excipients used in the product are well known. Droplet size distribution was tested with three batches of both strengths after production, and testing was repeated after 6 months storage at 40°C/75% RH in upright and inverted orientation. The results were compared with a batch of the originator product. The choices of the packaging and manufacturing process are justified. No clinical studies or bioequivalence studies were performed, as this is not required for a well-established use application.

Manufacturing process
The manufacturing process mainly consists of the preparation of the bulk solution, pre-filtration through a sterilizing filter, sterile filtration through a second sterilizing filter and filling into bottles. The process is performed under nitrogen. The sterile filtration is an acceptable method because degradation of dexpanthenol is more pronounced at higher temperatures and this limits the use of thermal methods of sterilisation. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot- scale batches per strength. The product is manufactured using conventional manufacturing techniques.

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

Quality control of drug product
The product specification includes tests for appearance, pH, osmolality, density, coloration, identity, assay, related substances, average mass, uniformity of mass and sterility. Except for related substances the release and shelf-life requirements are identical. A test for number of actuations per container should be added, and certain limits should be tightened. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches per strength stored at 25°C/60% RH (6 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 10 ml amber glass bottles with spray pump in inverted and upright position. At both storage conditions an increase of impurities was seen that was more pronounced at accelerated conditions. Stability data has been provided demonstrating that the product remains stable for 6 months following first opening of the container, when stored at 25°C/60% RH. No shelf life was granted yet, as insufficient stability data were provided.

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 HCl and dexpanthenol are well known. Both are widely used, well-known active substances. 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.

**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 HCl or dexpanthenol 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

Dexpanthenol and xylometazoline HCl are considered to be well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.
In addition, two studies were submitted in order to substantiate the use of dexpanthenol in the combination product.

**Pharmacokinetics**
No human pharmacokinetic data are available for xylometazoline as the analytical assays were not sensitive enough to detect xylometazoline in human plasma following nasal administration. In the clinical overview, the applicant refers to pharmacokinetics of xylometazoline in animals as no data in humans are available. This is sufficient for the well-established use application of xylometazoline nasal spray. In SPC section 5.2 it is correctly described that there are no pharmacokinetic data in humans, but that xylometazoline is systemically available to some extent based on reported side effects.

Dexpanthenol, or provitamin B5, is the alcohol analog of and a precursor to pantothenic acid (vitamin B5). Pantothenic acid itself is unstable in topical formulations and has therefore been replaced by dexpanthenol. Absorbed dexpanthenol is converted to pantothenic acid by alcohol dehydrogenase. Pantothenic acid is a component of coenzyme A (CoA) and phosphopantetheine, which are involved in fatty acid metabolism and the synthesis of cholesterol, steroid hormones, and all compounds formed from isoprenoid units. In addition, pantothenic acid is involved in the acetylation of proteins. It is shown that dexpanthenol is orally well absorbed and is also absorbed by the skin. In human plasma, pantothenic acid concentration ranges between 100 and 200 ng/mL. There is no information on the absorption of dexpanthenol into and across the nasal mucosa in animals or humans. This is acceptable as humans obtain pantothenic acid from a dietary source and a bacterial source; the latter is provided by the normal microflora of the large intestine and is absorbed in that region of the gut.
Dexpanthenol may act as an absorption enhancer. Increased absorption of xylometazoline is, however, not an intended effect. The applicant should ensure that the systemic exposure to xylometazoline is not increased.

No pharmacokinetic data of the xylometazoline-dexpanthenol combination product has been provided.

**Pharmacodynamics**
Xylometazoline
There is no information on the nasal dose relationship with the decongestant effect of xylometazoline. It was demonstrated by Aschan and Drettner (1964) that the constricting effect of xylometazoline was more pronounced and had a longer duration than that of ephedrine. This effect applied both to the healthy subjects and to those with acute rhinitis, and the difference in effect between the two preparations was statistically significant in both groups of subjects.
The decongestant effect of xylometazoline was well maintained at 6 hours post-dose, and recordings over a longer period showed that the effect lasted about 12 hours both in healthy subjects and acute rhinitis patients.

Dexpanthenol
Dexpanthenol is the alcohol analog of a precursor to pantothenic acid (vitamin B5). In pharmaceutical technology, panthenol is used as a skin penetration enhancer, e.g. for increasing the transdermal absorption of progesterone (Valenta and Dabic 2000). In cosmetics, because panthenol is water soluble and hygroscopic, it has skin moisturisation potential (Gloor et al 2002, Wollina and Kibicki 2007).

Wound healing efficacy in sinus mucosa has been demonstrated in animal experiments and is described in the non-clinical overview provided.

Combination of xylometazoline with dexpanthenol

In a study by Verse et al. (2003) dexpanthenol reduced cytotoxicity of xylometazoline resulting in a cell growth rate of 84% of control as compared to between 6 and 20% in the presence of xylometazoline only.

In a study by Klöcker et al. (2003) 5% dexpanthenol statistically significantly reduced the concentration-dependent toxic effects of xylometazoline on human-amnion-cell growth. It also showed repairing effect of dexpanthenol on decreased frequency of mucociliary apparatus in isolated human nasal mucosal cells caused by xylometazoline. Dexpanthenol reduced the inhibition of ciliary beat frequency caused by 0.1% xylometazoline.

In a study by Klöcker et al. (2004) dexpanthenol proved to have a great protective effect on cells and smaller therapeutic effect. Two test series of the study evaluated (a) protective effect (first, 5-minute incubation with dexpanthenol and, thereafter, rinsing for 5 minutes with Ringer's solution and another incubation for 5 minutes with xylometazoline) or (b) therapeutic effect (vice versa incubation scheme) of dexpanthenol on xylometazoline, and all controlled by placebos and Ringer's solution. The study showed dexpanthenol had a great protective effect on cells when applied prior to xylometazoline (first series, cell growth for xylometazoline after dexpanthenol vs. xylometazoline after placebo $p<0.001$). It also had therapeutic effect (second series) when applied after xylometazoline (this effect was, however, 30-50% weaker than the protective effect). This study showed neither xylometazoline nor dexpanthenol had time dependent effect on cells.

The effect of dexpanthenol addition among four comparable nasal spray formulations is demonstrated by the results in Table 1.

**Table 1 Cytotoxicity (relative cell growth) of preservative-free nasal sprays containing 0.1% xylometazoline hydrochloride with or without 5% dexpanthenol (Verse et al. 2003)**

| *Name* | *Dexpanthenol* | *pH* | *Osmolality* | *Cell growth (% of control)* |
|---|---|---|---|---|
| Xylometazoline + Dexpanthenol (not yet marketed) | 5% | 5,58 | 422 | 84 |
| Otriven OK | 0 | 5,79 | 274 | 20 |
| Olynth OK | 0 | 5,86 | 295 | 17 |
| Nasenspray E | 0 | 5,75 | 274 | 6 |

The addition of dexpanthenol to xylometazoline is not investigated on a pharmacodynamic endpoint, but only on *in vitro* ciliotoxicity.

**Clinical efficacy**

The use of xylometazoline in the treatment of nasal congestion in rhinitis associated with the common cold, allergic rhinitis, and sinusitis is considered well-established and is sufficiently described in the clinical overview.

The use of dexpanthenol in the treatment of nasal congestion of rhinitis and sinusitis is considered not well-established at this moment.

The applicant provided two clinical studies to support the rationale for use of dexpanthenol in the xylometazoline/dexpanthenol combination in the claimed indication 'and as supportive treatment allowing better tolerability and shorter treatment with xylometazoline alone.'

The applicant provided one study demonstrating the effect of dexpanthenol in patients with rhinitis sicca. Xylometazoline is contra-indicated in the treatment of rhinitis sicca. Rhinitis sicca is not included in the target population of this combination therapy. This study is therefore not discussed.

**Pivotal study: Acute non-allergic rhinitis**

The efficacy of the combination of xylometazoline with dexpanthenol is investigated in 151 patients with acute non-allergic rhinitis.

Using a statistically confirmatory, double-blind, active-controlled, parallel-group trial design, outpatients with acute rhinitis, aged between 18 and 70 years, were randomized to either xylometazoline nasal spray, 1 mg/ml, (N=76) or to a nasal spray formulation containing both xylometazoline 1 mg/ml and dexpanthenol 50 mg/mL (N=75) (Kehrl et al. 2003).

Patients suffered from acute rhinitis defined by a sum score ≥ 6 derived from four symptoms (nasal obstruction, rhinorrhea, turbinate hyperplasia, and mucosal redness), each graded as 0=none, 1=minor, 2=moderate, 3=strong, and 4=very strong. Duration of treatment was 5 days with 3 times daily dosing, each dose consisting of one actuation of 100 µL into each nostril.

The sum score for the four symptoms listed above constituted the primary efficacy parameter. The symptomatic improvement from baseline was statistically significant at day 5 for each of the four variables in favor for the combination therapy (p<0.01) (Table 2)

**Table 2: Primary efficacy scores (means ± SD) during 5 days of treatment**

| | Xylometazoline (N=76) | | | Xylometazoline plus dexpanthenol (N=75) | | | |
|---|---|---|---|---|---|---|---|
| **Symptom** | **Baseline** | **3 days** | **5 days** | **Baseline** | **3 days** | **5 days** | **P value*** |
| Nasal obstruction | 2.3±0.5 | 1.7±0.5 | 1.3±0.6 | 2.3±0.6 | 1.0±0.6 | 0.6±0.6 | <0.0001 |
| Rhinorrhea | 2.4±0.6 | 1.9±0.7 | 1.5±0.8 | 2.3±0.8 | 1.2±0.7 | 1.0±0.8 | 0.0011 |
| Mucosal redness | 2.6±0.8 | 2.2±0.5 | 1.7±0.8 | 2.5±0.7 | 1.1±0.5 | 0.7±0.7 | <0.0001 |
| Turbinate hyperplasia | 2.3±0.6 | 1.8±0.6 | 1.5±0.7 | 2.6±0.7 | 1.2±0.6 | 0.6±0.7 | <0.0001 |

*P value relates to the difference between monotherapy and combination therapy

Secondary efficacy parameters were mucosal congestion, rhinoscopic status, external nasal irritation, mucosal dryness and scab formation improvement from baseline.

**Secondary efficacy scores (means±sd) during 5 days of treatment**

| | | Xylometazoline | | | Xylometazoline+Dexpanthenol | | |
|---|---|---|---|---|---|---|---|
| | N | Score | Change | N | Score | Change | P |
| *A*=mucosal congestion: | | | | | | | |
| 0 (base line) | 76 | 2,3±0,6 | – | 76 | 2,4±0,6 | – | |
| 3 | 76 | 2,0±0,3 | −0,3±0,6 | 75 | 1,4±0,6 | −1,0±0,7 | <0,0001 |
| 5 | 76 | 1,6±0,7 | −0,7±0,9 | 75 | 0,8±0,8 | −1,6±1,0 | <0,0001 |
| *B*=rhinoscopic status: | | | | | | | |
| 0 (base line) | 76 | 2,5±0,8 | – | 76 | 2,5±0,6 | – | |
| 3 | 76 | 2,1±0,5 | −0,4±0,8 | 75 | 1,2±0,4 | −1,3±0,7 | <0,0001 |
| 5 | 76 | 1.7±0.7 | −0,8±0,9 | 75 | 0,7±0,6 | −1,8±0,8 | <0,0001 |
| *C*=external nasal irritation | | | | | | | |
| 0 (base line) | 76 | 2,2±0,9 | – | 76 | 2,3±0,8 | – | |
| 3 | 76 | 2,0±0,6 | −0,2±1,0 | 75 | 0,9±0,8 | −1,4±1,1 | <0,0001 |
| 5 | 76 | 1,4±0,9 | −0,8±1,3 | 75 | 0,6±0,8 | −1,7±1,0 | <0,0001 |
| *D*=nasal dryness | | | | | | | |
| 0 (base line) | 76 | 0,5±0,9 | – | 76 | 0,8±1,1 | – | |
| 3 | 76 | 1,7±0,9 | +1,2±1,2 | 75 | 0,3±0,7 | −0,5±1,2 | <0,0001 |
| 5 | 76 | 1,2±1,0 | +0,7±1,1 | 75 | 0,4±0,7 | −0,4±1,2 | <0,0001 |
| *E*=scab formation. | | | | | | | |
| 0 (base line) | 76 | 0,3±0,7 | – | 76 | 0,4±0,8 | – | |
| 3 | 76 | 1,4±1,0 | +1,1±1,1 | 75 | 0,2±0,5 | −0,2±0,8 | <0,0001 |
| 5 | 76 | 0,9±1,0 | +0,6±1,1 | 75 | 0,3±0,6 | −0,1±0,9 | <0,0001 |

*P values demonstrate relate to the difference between xylometazoline and xylometazoline/dexpanthenol

At day 3, the difference between the secondary parameters was statistically significant for all parameters. For the 'pure' nasal decongestant xylometazoline, the scores for nasal dryness and scab formation increased, which are known side effects of xylometazoline. This effect was ameliorated by concomitant dexpanthenol treatment as evidenced by the decreasing scores. Reduction of nasal dryness by the

addition of dexpanthenol could be a therapeutic advantage of the combination spray.

The applicant performed an additional analysis aimed to support the claim of a shorter treatment duration: Faster response is defined as shorter time (in terms of days) to decrease of symptom-scores. In the xylometazoline group the nasal-obstruction score was reduced from 2.3 ± 0.5 at the baseline to 1.3 ± 0.6 in 5 days of treatment, while in the combination-group the same endpoint was reduced from 2.3 ± 0.6 at the baseline to 1.0 ± 0.6 in 3 days of treatment.

**Supportive study: Rhinitis after nasal surgery**
The study of Kehrl and Sonneman (2000) was a randomized double blind active controlled parallel group study in 61 patients were treated with either xylometazoline 0.1% spray or with xylometazoline 0.1% combined with 5% dexpanthenol for 14 days following nasal surgery.

The primary efficacy parameter was defined as the improvement of the subjective sense of nasal obstruction. Secondary parameters included the extent of pharyngitis, mucosal swelling and bleeding during the post-surgical wound care.

61 patients were included (22 female, 37 male), mean age 37 years old. The results for the mean score for the nasal obstruction are shown in Table 3.

Table 3 Mean nasal obstruction scores after nasal surgery during 14 days of nasal spray treatment with either xylometazoline of xylometazoline/dexpanthenol combination.

| Treatment day | Xylometazoline (n=30) | | Xylometazoline-dexpanthenol (n=30) | |
|---|---|---|---|---|
| | | *(SD)* | | *(SD)* |
| Baseline | 4.02 | 0.99 | 3.90 | 1.09 |
| 1 | 3.63 | 1.13 | 3.93 | 1.11 |
| 4 | 3.20 | 1.16 | 2.97 | 096 |
| 7 | 2.33 | 0.84 | 1.90 | 0.66 |
| 14 | 2.07 | 0.74 | 1.90 | 0.48 |

Nasal obstruction improved from day 1 to 7 by 1.3 score units with xylometazoline spray and by 2.0 score units with combination therapy (p=0.0316). This was maintained at day 14.
No significant difference including bleeding during the post surgical wound care, between the groups were seen for secondary efficacy parameters or local tolerability. The effect on the skin and mucosal healing of the nose was not described.

In this study the improvement of symptoms related to nasal congestion is larger in the fixed dose group using xylometazoline/dexpanthenol compared with xylometazoline alone. However it is not known how this will be perceived by patients. The effect on nasal dryness has not been reported.

**Conclusion regarding efficacy**
The use of xylometazoline in the symptomatic treatment of nasal congestion due to rhinitis and sinusitis is considered well-established. The role of dexpanthenol in this patient group is not clear.
No literature regarding the use of dexpanthenol monotherapy in the treatment of rhinitis and sinusitis has been provided. In addition, no literature has been provided demonstrating the beneficial effect of dexpanthenol as “step up therapy” in the (supportive) treatment of nasal congestion due to rhinitis or sinusitis. Literature demonstrating the use c.q. beneficial effect of dexpanthenol monospray in order to improve the tolerability of the adverse events of xylometazoline is also lacking. In addition, the provided studies do not investigate the role of dexpanthenol monotherapy in the proposed broad target population.

The number of studies establishing the use of the combination therapy was limited to two clinical studies. One randomised controlled parallel study in 151 adult patients suffering from acute non-allergic rhinitis is included. One additional study included patients suffering from rhinitis after nasal surgery. This is considered a rare cause of rhinitis and of limited value to support the claimed indication.

In both studies, a statistically improvement of nasal congestion was observed with xylometazoline-dexpanthenol compared to xylometazoline alone.
The clinical relevance of this finding requires further discussion, because no data has been provided demonstrating that this difference will be perceived by patients and thus could lead to a reduced duration of treatment. For example, in the main study, the absolute difference in nasal congestion was 0.7 at day 5, while a perceivable improvement needs to be a one point improvement in gradation score. It seems unlikely that this difference will be perceived.

In the pivotal study, the four main endpoints were related to the effects of xylometazoline. The improvement was statistically significant in favor of xylometazoline-dexpanthenol. No comparison was being made with dexpanthenol monotherapy. It is therefore not clear, whether the improvement is due to an additive effect of dexpanthenol or if dexpanthenol increases the local exposure to xylometazoline.

In the pivotal study, xylotmetazoline-dexpanthenol improved the secondary parameters, like nasal dryness and scab formation, while this was not described-reported in the supportive study in patients suffering from rhinitis after surgery. Up till now, this is the *only* study demonstrating that dexpanthenol could have this effect in patients. More studies are needed, preferably in the proposed target population.

The applicant provided an additional *post hoc* analysis aimed at proving that a faster improvement was observed with the combination therapy. *Post hoc* analysis can be regarded as hypothesis generating and should be confirmed with a prospectively performed study

No literature has been provided regarding the use of xylometazoline-dexpanthenol in allergic rhinitis, or sinusitis, although they are considered important target groups. In addition, no efficacy data in children for the lower dose combination has been described. Important efficacy data for a large target population is therefore missing.

In conclusion, the two studies described in the clinical overview provide insufficient support for the claimed efficacy and tolerability of the proposed indication for the fixed dose combination.

**Clinical safety**
European population exposure to xylometazoline nasal formulations has been extensive and sufficient for demonstrating safety.

Due to interaction, xylometazoline may only be used after careful consideration of the risks and benefits in the following cases in patients treated with monoamine oxidase inhibitors (MAO inhibitors) or other medicinal products with a potentially hypertensive effect.

Conditions in which caution is also necessary are:
- increased intraocular pressure, particularly narrow-angle glaucoma
- severe cardiovascular disorders (e.g. coronary heart disease, hypertension)
- phaeochromocytoma (adrenal tumour)
- metabolic disorders (e.g. hyperthyroidism, diabetes mellitus)
- porphyria
- prostatic hyperplasia

Dexpanthenol exposure is known of combination nasal sprays licensed in a limited number of European countries. Dexpanthenol is also added to saline solutions in nasal sprays also available for young children. There have been a few reports of allergic reactions possibly associated with dexpanthenol (Martindale 2011a). Systemic dexpanthenol is contra-indicated in haemophiliacs and in patients with ileus due to mechanical obstruction.

Xylometazoline/dexpanthenol
The safety base of the fixed dose combination is based on the two provided studies described in the clinical overview. Only few and minor adverse events (AEs) were associated with the combination nasal spray in the two clinical trials including in total 212 adult patients, with 106 exposed patients to

xylometazoline/dexpanthenol 1.0/50 mg/ml.
In the main study, there were 5 AEs in the xylometazoline group (epistaxis, N=4; burning feeling durch spray application, N=1) and there was one AE within the combination group (minor blood tinged nasal secretion). No safety concerns arose from clinical laboratory investigations, clinical checkups, rhinoscopy or nasal tolerability. In the supportive study, adverse events were not reported.

No safety of the 0.5/50 mg/mL combination has been provided in children.
In addition, no safety data from a large target population e.g. patients with allergic rhinitis and sinusitis has been included either. Also, no post marketing data have been provided.

**Discussion regarding safety**
No additional safety issues than already known of xylometazoline are described apart from allergic reactions. The improvement in symptoms score related to nasal congestion is larger in the patient group exposed to xylometazoline/dexpanthenol. This raises concerns regarding a higher exposure to xylometazoline, which could be eliminated by for example a sufficient safety database.
In the clinical overview it is mentioned that only few and minor AEs were associated with the combination nasal spray in the two clinical trials, but the number of exposed patients is low (n=106) and does not include the whole target population i.e. patients with allergic rhinitis, sinusitis and children.
In the clinical studies only a few adverse events were mentioned in both treatments, therefore a conclusion regarding the better tolerability of the fixed dose combination is difficult to make.
No children are included in this safety data base and children are considered more vulnerable to side effects.

**Rationale for the fixed dose combination xylometazoline-dexpanthenol**
Normally the justification for using a fixed dose combination will be a simplification of therapy or an improvement of a benefit-risk due to *e.g*. counteracting by one substance of an adverse reaction produced by another.

Usually, monotherapy is started for treatment of a medical condition. If insufficient improvement is observed, another treatment is added, *i.e.* add on therapy. If these treatments are often used concurrently, therapy can be simplified by use of a fixed dose combination, *i.e.* substitution therapy.

Add on
Xylometazoline is an established monotherapy in the treatment of rhinitis and sinusitis. Dexpanthenol has presently not been indicated in the treatment of rhinitis and sinusitis, and is not being used as “add on” therapy in the treatment of nasal congestion to improve the efficacy. In the clinical study no patient population has been defined which will obtain clinical benefit from the addition of dexpanthenol in the treatment of nasal congestion.

Combining two treatment which are often given concurrently: substitution therapy
No well-established role for dexpanthenol as “add on” therapy to treat the nasal dryness induced by xylometazoline has been described. No literature was provided demonstrating that dexpanthenol is often combined with xylometazoline to reverse its side effects. The fixed dose combination can therefore not be used as substitution therapy, as these individual products are not often given concurrently.

Better benefit/risk profile of the combination: better efficacy/counteracting adverse events
Another justification for the fixed dose combination could be that it provides a better benefit/risk ratio.
According to the applicant *a level of efficacy above the one achievable by a single substance (shortening of disease duration) with an acceptable safety profile* and *counteracting by one substance* (dexpanthenol) *of an adverse reaction produced by another one,* i.e. nasal dryness induced by xylometazoline, and the combination of xylometazoline hydrochloride with dexpanthenol in one spray formulation results in a significant *simplification of therapy.*

The applicant argues that the faster clinical response of nasal mucosa may reduce the incidence of rhinitis medicamentosa. Indeed, the difference in the sum of the clinical symptom score was statistically different at day 5 in the submitted study but it is not known if this is perceived by patients as such. No literature has

been provided demonstrating that patients will use xylometazoline/dexpanthenol for a fewer days to treat symptoms than xylometazoline monotherapy. No literature was provided demonstrating that the *incidence* of rhinitis medicamentosa is lower with the use of xylometazoline/dexpanthenol compared to with xylometazoline-monotherapy. The clinical relevance of the statistically better improvement of nasal symptom score is therefore still uncertain. Consequently, the beneficial effects of the addition of dexpanthenol regarding the efficacy of xylometazoline are therefore questionable.

Another claimed benefit might be a better tolerability of the combination therapy compared with xylometazoline monotherapy. Fewer side effects were observed, but the safety database is small (n=106). A reduced nasal dryness and scab formation was observed/reported with xylometazoline-dexpanthenol as compared to xylometazoline alone in one study, but not confirmed in another one. According to the applicant, this effect is due to the moistening effect of dexpanthenol.
As mentioned before, no data were provided demonstrating how many patients stop treatment due to the side effect nasal dryness and how this affects the overall patients' satisfaction with treatment.
In addition, the need for counteracting this side effect by adding dexpanthenol needs to be substantiated, because this side effect may actually prevent prolonged use.. The beneficial effects of the addition of dexpanthenol to xylometazoline regarding the safety are therefore still insufficiently demonstrated.

In conclusion, the member states consider the role of this fixed dose combination "For temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis allowing better tolerability and shorter treatment than xylometazoline alone" neither well defined nor well-established in the treatment of nasal congestion due to rhinitis and sinusitis.

**Benefit/risk assessment**
A bibliographical application requires demonstration that the product applied for has a *well-established use* with recognized efficacy and safety in the claimed indication. A proper rationale must be provided based of published information.

Benefits
*Beneficial effects*
The main trial is a randomised, double blind, parallel study (Kehrl 2003) testing a 5-day treatment with a nasal spray containing 5 mg dexpanthenol/0.1 mg xylometazoline combination for patients with acute non-allergic rhinitis; 151 patients were included. A statistically significant improvement in the primary efficacy score (*i.e*. nasal obstruction, rhinorrhoea, turbinate hyperplasia, and mucosal redness) was observed with xylometazoline/dexpanthenol on day 5 ($p<0.0001$). Also a reduction in nasal dryness and scab formation was observed with xylometazoline/dexpanthenol.

Further reference to efficacy and safety of the product has been mainly based on the clinical properties of xylometazoline nasal spray without the addition of dexpanthenol.

*Uncertainty in the knowledge about the beneficial effects*
The effect was only demonstrated in one small trial in 151 patients. The strength of the effect was not quantified in this study, precluding an assessment of the precision of the reported effect. Insufficient information was reported to judge whether the trial was of sufficient methodological quality (Kehrl et al. 2003).

Kehrl et al. investigated the effect of xylometazoline/dexpanthenol 0.1%/5% in rhinitis. Although a significant improvement of symptom score was observed as compared with xylometazoline alone, the clinical relevance of this finding is not clear, *e.g.* it is not known if this difference in nasal symptom score will be perceived by patients and will lead to reduced treatment duration.

A supportive study included a randomised, double blind study for the treatment of rhinitis after nasal surgery and included 60 patients (Kehrl and Sonneman 2000). The mean nasal obstruction scores showed statistically significant improvement with the combination product after nasal surgery. The difference was significant from day 7 onwards ($p=0.0316$). No information regarding the reduction of nasal dryness has been provided.

In the clinical studies, the parameter “duration of treatment” was neither included as a primary, nor as a secondary parameter.

No literature has been provided demonstrating a better tolerability and shorter treatment duration, *i.e.* fewer days of treatment, with xylometazoline/dexpanthenol compared to xylometazoline monotherapy.

A reduction in nasal dryness was only observed and reported in the main study and is not confirmed by the supportive study.

Although the applicant claims that dexpanthenol has an independent pharmacological action and does not enhance the effect of xylometazoline, no convincing data are provided to support this claim.

The effect of dexpanthenol monotherapy on rhinitis and sinusitis has not been investigated.

No studies have been provided demonstrating the efficacy and safety of the xylometazoline-dexpanthenol combination in allergic rhinitis and sinusitis.

No studies in children have been provided demonstrating the efficacy and safety of the lower dose combination xylometazoline/dexpanthenol, *i.e.* 0.05%/5%.

Dexpanthenol does not have an indication for in the treatment of rhinitis, sinusitis, as monotherapy, or as “add on” therapy. Also, no patient population has been identified which would benefit from the combination treatment. Therefore, the rationale for this fixed dose combination cannot be substitution therapy in order to improve compliance.

The applicant stated that this combination product provides a better efficacy and safety than monotherapy with the individual components and could be used to reverse the adverse events induced by xylometazoline. Unknown is how many patients stop xylometazoline treatment due to nasal dryness and how many patients use dexpanthenol to treat the side effects of xylometazoline. Hypothetically, eliminating the side effects may lead to a prolonged exposure to xylometazoline.

Risks

*Unfavourable effects*

The combination of xylometazoline/dexpanthenol demonstrated a faster improvement on symptoms related to the effect of xylometazoline: nasal obstruction, mucosal redness and turbinate hyperplasia. This may indicate that the absorption of xylometazoline is enhanced, which raises concerns regarding the local and systemic exposure which may affect the safety profile, especially in children.

*Uncertainty in the knowledge about the unfavorable effects*

The applicant provided safety data of xylometazoline and dexpanthenol alone. The provided safety data of the combination therapy is limited: safety data of 106 exposed patients who were enrolled in the two studies were provided. No safety data from patients suffering from allergic rhinitis and sinusitis were included, while this might be a large target population.

No safety data of children and adolescents were provided. No safety data of the lower dose combination was provided. No post marketing data was submitted.

Benefit- Risk Balance

The applicant applied for the following indication: “for temporary symptomatic treatment of nasal congestion due to rhinitis and sinusitis and supportive treatment allowing better tolerability and shorter treatment with xylometazoline alone” based on Directive 10a, well-established use.

According to the applicant, the rationale of the fixed dose combination is that it demonstrated a level of efficacy above the one achievable by a single substance (by shortening of disease duration) with an acceptable safety profile and the counteracting of one substance (dexpanthenol) on an adverse reaction

induced by another, *i.e.* nasal dryness induced by xylometazoline, resulting in a significant simplification of therapy

Xylometazoline has a well-established role in the symptomatic treatment of nasal congestion due to rhinitis and sinusitis, while dexpanthenol does not: nor as “ad on therapy” nor as therapy to reverse the adverse events induced by xylometazoline. The use of dexpanthenol in the treatment of nasal congestion due to rhinitis and sinusitis is not considered well-established.

In the clinical overview, the number of clinical studies to support the claimed indication of the combination therapy was limited to two: one main study in 151 adult patients suffering from acute non-allergic rhinitis and one study in patients suffering from rhinitis after nasal surgery. This is considered a rare cause of rhinitis and of limited value to support the claimed indication. The efficacy parameters are therefore mainly derived from one study, where no comparison was being made with dexpanthenol monotherapy. It is therefore difficult to establish if a level of efficacy was achieved above the one achievable by a single substance, although a concern exists that dexpanthenol can enhance xylometazoline exposure.
No primary or secondary efficacy parameter “duration of treatment” was included in the clinical studies to support that a shorter duration of treatment can be achieved with the combination therapy
Although a greater improvement was statistically significant observed in nasal symptoms score, the clinical relevance of this finding is not clear. It is for example not known if patients notice this difference in clinical improvement and if this will effectively lead to a reduction in treatment days.
No additional literature has been provided to support the claim that the efficacy will result in a shortening of treatment duration.

The improved effect on nasal dryness was only observed in one study and not confirmed by the other. The claimed counteracting effect should be confirmed in another study especially because the indication included a variety of disease conditions.
The necessity for counteracting the side effects of xylometazoline, *e.g*. nasal dryness has to be substantiated because it may in fact prevent patients from prolonged use of the xylometazoline, making the safety profile of the fixed dose combination different from xylometazoline monotherapy. However, the adverse event rate was low in both studies, making it difficult to support the claim that the combination therapy is better tolerated, especially as there is a concern that dexpanthenol may increase the exposure to xylometazoline. No systemic side effects were observed. However, the safety database is limited to 106 exposed patients and did not include the whole target population. No children were included, while children are the most vulnerable patients to the systemic side effects.
No literature regarding the use of the lower dose in children in the proposed indication has been provided.

Dexpanthenol has no established use in the treatment of nasal congestion. The claimed rationale for adding dexpanthenol to xylometazoline has to be obtained from the clinical studies. The clinical relevance of the improved nasal symptom score has not been demonstrated i.e. the submitted studies do not support the claim that the combination therapy results in a shorter treatment duration. The clinical studies also insufficiently support the acclaimed better tolerability. No patient population has been defined which will benefit from the addition of dexpanthenol to xylometazoline.

A basic requirement on the phase III documentation is that it consists of data of good quality from a sufficient number of patients, with a variety of symptoms and disease conditions (CPMP-EWP-2330-99). The provided literature for the applied indication is mainly based on one study including a subpopulation of the proposed target population (adults only), and a subgroup of the proposed indications (only acute non-allergic rhinitis was investigated). This is considered to be insufficient to claim well-established use of the fixed dose combination for the proposed indications.

In conclusion, for temporary symptomatic treatment of nasal congestion due to rhinitis and sinusitis and supportive treatment allowing better tolerability and shorter treatment with xylometazoline alone, the benefit-risk balance is negative and the product is therefore not approvable.

Risk management plan

As the application for these products was not approved; the evaluation of the risk management plan is no longer relevant.

**Product information**

SPC/package leaflet
Product information has not been determined, as the application was withdrawn.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The RMS, on the basis of the data submitted, considered that Xylometazoline HCl/Dexpanthenol 0.5/50 mg/ml ratiopharm, nasal spray, solution and Xylometazoline HCl/Dexpanthenol 1.0/50 mg/ml ratiopharm, nasal spray, solution have not demonstrated a satisfactory risk/benefit profile (see also discussion below).

The indication applied for was *temporary symptomatic treatment of nasal congestion due to rhinitis or sinusitis and as supportive treatment allowing better tolerability and shorter treatment than xylometazoline alone.*

A potential serious risk to public health (PSRPH) was identified, which pertains that the provided literature is considered insufficient to support the claimed indication based on well-established use. Dexpanthenol has no established use in the treatment of nasal congestion. The clinical relevance of the improved nasal symptom score when adding dexpanthenol to xylometazoline has not been demonstrated, *i.e.* the submitted studies do not support the claim that the combination therapy results in a shorter treatment duration. The clinical studies also insufficiently support the claimed better tolerability. No patient population has been defined which will benefit from the addition of dexpanthenol to xylometazoline.

In the Board meeting of 11 April 2012, as discussion was held regarding the rationale for including dexpanthenol in the fixed dose combination. The benefit-risk balance was considered negative. In the Board meeting of 9 January 2013, it was concluded that the data to support the sought indication are deemed to be insufficient. Therefore no benefit of the combination compared to the monotherapy could be established.

Considering this assessment, the applicant decided to withdraw the application before finalisation of the decentralised procedure. No marketing authorisation has been granted. The procedure ended on 15 January 2013.

## 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 |
|---|---|---|---|---|---|---|
| | | | | | | |

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