Public Assessment Report

Scientific discussion

Oxymetazoline HCl 0.5 mg/ml Focus, nasal spray, solution

(oxymetazoline hydrochloride)

NL License RVG: 112057

Date: 3 June 2019

This module reflects the scientific discussion for the approval of Oxymetazoline HCl 0.5 mg/ml Focus, nasal spray, solution. The marketing authorisation was granted on 19 January 2015. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.

A list of literature references is given on page 10.
# List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BKC</td>
<td>Benzalkonium chloride</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
</tr>
<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloride</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>RH</td>
<td>Relative Humidity</td>
</tr>
<tr>
<td>RM</td>
<td>Rhinitis Medicamentosa</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Oxymetazoline HCl 0.5 mg/ml Focus, nasal spray, solution from Focus Care Pharmaceuticals BV.

The product is indicated for local symptomatic relief of nasal congestion in adults and children aged 6 years and over.

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

This application concerns a bibliographical application based on well-established medicinal use of oxymetazoline HCl nasal spray. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated 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.

Oxymetazoline has been marketed for over 40 years. Nasal sprays containing oxymetazoline 0.05% are registered by several different MAHs in the Netherlands for the symptomatic relief of nasal congestion.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Oxymetazoline HCl 0.5 mg/ml Focus is a colourless solution. The nasal spray contains 0.5 mg/ml oxymetazoline hydrochloride, corresponding to 0.44 mg/ml oxymetazoline. Per spray (0.07 ml) 35 mcg oxymetazoline is delivered.

The solution is packed in a nebulizer bottle with a dosing pump which constitutes both the reservoir for the dose to be administered, and the administering device. Each bottle contains 15 ml of solution. The nebulizer bottle is made of high density polyethylene, while the dosing pump is made up of three pieces: cap (low density polyethylene), nasal applicator (polypropylene) and dosing pump (polypropylene).

The excipients are benzalkonium chloride, anhydrous disodium phosphate (E339), dihydrate monosodium phosphate (E339), glycine (E640), sorbitol (non-crystallizable) (E420), purified water.

II.2 Drug Substance

Oxymetazoline hydrochloride is an established active substance described in the European Pharmacopeia (Ph.Eur.). The substance is a white or almost white hygroscopic crystalline powder which is freely soluble in water and in ethanol and practically insoluble in ether.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.
Quality control of drug substance
The drug substance specification is in line with Ph.Eur. and the additional parameters as mentioned on the CEP. 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.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described in sufficient detail. The functions of the excipients are explained. Sufficient data have been provided with regard to minimum fill, extractables and leachables, actuator deposition, initial & re-priming requirements, cleaning requirements, performance after temperature cycling, robustness and delivery device development.

The antimicrobial preservative benzalkonium chloride is a well known preservative usual for this type of product. The concentration of 0.02% is common and has been demonstrated to be adequate. For this well established use application it must be demonstrated that the proposed formulation is comparable to currently registered products, and is not expected to result in different properties compared to already approved products. The MAH provided comparative data between Nasivin 0.5 mg/ml nasal spray (NL License RVG 19073) and the product applied for. Based on the data provided both products are considered comparable. The limits for osmolality (310-350 mOsm/kg) and pH (5.5-6.5) are justified.

Manufacturing process
The manufacturing process involves the following steps: dissolving of the active substance and excipients in purified water, homogenization, making up of volume with purified water, filtering of the solution, and packaging. The process has been described in sufficient detail. Process validation data have been provided for three production scaled batches. The manufacturing process has been adequately validated.

Control of excipients
All excipients are described in the Ph.Eur. and have been tested accordingly. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for organoleptic characteristics, uniformity of dosage units, mean delivered dose, mean volume, pH, osmolality, identification and assay of benzalkonium chloride and oxymetazoline hydrochloride, oxymetazoline related substances, microbial contamination and droplet size. The release and end-of shelf-life specifications are identical, with the exception of pH, assay of active substance and related substances. Limits have been justified. The analytical methods have been adequately described and validated. Batch analysis data has been provided on three industrial batches of the drug product, demonstrating compliance with the batch release specification.

Stability of drug product
The MAH submitted stability data at long term storage conditions (25°C/40% RH) of two pilot batches up to 24 months, and three industrial scale batches up to 36 months. At intermediate storage (30°C/65% RH) 12 months data has been provided for all pilot and industrial scale batches. Up to 6 months accelerated data (40°C/15% RH) is available for the two pilot scale batches. The product was packed in the proposed package. The conditions used in the stability studies are according to the ICH stability guideline.

In the stability results of industrial scale batches, all results meet specifications. A photostability test in line with the Note for Guidance on Photostability testing of New Active Substances and Medicinal Products has been performed. The drug product was demonstrated to be photostable. Based on the stability data, a shelf life of 24 months has been granted. The product should be stored below 30°C.
An in-use stability study has been performed with two production scaled batches at initial and at 30-day time points. Both batches complied after 30 days with the shelf life specification. The in-use shelf life of 30 days is acceptable.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Oxymetazoline HCl 0.5 mg/ml Focus, nasal spray, solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of oxymetazoline are well known. As oxymetazoline 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 preclinical pharmacology, pharmacokinetics and toxicology. This overview is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The product is likely to replace existing marketed oxymetazoline containing products. The approval of this product will not result in an increase in the total quantity of oxymetazoline 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. Further environmental risk assessment is therefore not considered necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

No clinical studies have been submitted to support this well-established use application. This is acceptable as oxymetazoline 0.5 mg/ml nasal spray is a topical decongestant for relief of nasal congestion to be administered intranasally, and various oxymetazoline nasal sprays 0.5 mg/ml products have been on the market for 40 years.

IV.2 Pharmacokinetics

Oxymetazoline Focus 0.5 mg/ml spray is an aqueous solution without excipients affecting the behaviour of the formulation in the nose. No pharmacokinetic studies have been submitted to support this application which is acceptable. Reference is made to other EU oxymetazoline 0.5 mg/ml products based on literature. The MAH has sufficiently justified that the elimination half life ranges form 5 to 8 hours.

IV.3 Clinical efficacy

The MAH provided an overview of clinical studies published between 1965 and 2010. Clinical studies referred to were heterogeneous: observational, controlled, non-controlled, randomized, and non-randomized trials. Comparators included placebo, xylometazoline, nafazoline and phenylephrine. In one study, the effect of oxymetazoline added to budesonide was investigated.
The efficacy studies included clinical endpoints such as secretion and nasal hyperemia in an ordinal scale of severity, global evaluation by the investigator, nasal symptoms in ordinal severity scale, objective response evaluated by the investigator, and amount of medication taken.

**Oxymetazoline efficacy studies**

The efficacy of oxymetazoline nasal spray has been shown in many controlled trials in patients with different conditions such as nasal congestion, nasal hyperaemia, rhinitis, common cold and epistaxis, as well as in healthy subjects.

**Slodki and Montgomery (1965)**

Symptomatic treatment of nasal congestion was evaluated in the publication “Clinical comparison of oxymetazoline and ephedrine in nasal decongestion”.

In a trial done in 99 male patients from 18 – 49 years old with rhinorrhea and nasal mucosa hyperaemia associated with upper respiratory duct virus infection, patients were distributed in three groups which received treatment with oxymetazoline drops 5%, oxymetazoline spray 5% and an ephedrine 1% solution, respectively. Patients were examined at baseline and after 30 min. At those 30 min. nasal hyperaemia reduction with ephedrine, oxymetazoline drops and oxymetazoline spray was 0.25, 0.28 and 0.68 respectively, while the reduction in nasal secretion was 0.37, 0.49 and 0.82, respectively. At 24 hours, nasal hyperaemia reduction data were 0.18, 0.25 and 0.40 respectively. Regarding the reduction in nasal secretion, data were 0.42, 0.54 and 0.38.

Major effectiveness of oxymetazoline spray was shown compared to oxymetazoline drops, after 24 hours and especially after 30 minutes.

**Voss et al. (1973)**

In a randomized, double-blind, controlled clinical trial with phenirephrine, 98 patients from 5 – 60 years old with allergic or infectious rhinitis, received treatment with oxymetazoline spray 0.05% or phenylephrine spray 0.5%. The evaluation by the investigators was good or excellent in 75% and 53% of the patients treated with oxymetazoline or phenylephrine respectively. The same results were obtained in the evaluation by the patients.

**Miller (1964), Neffson (1968), Akerlund et al. (1989)**

In “Oxymetazoline in allergic rhinitis” (Miller 1964), patients with secondary nasal blockage were enrolled to be treated with oxymetazoline. Neffson (1968), in “A topical nasal decongestant for children”, tried oxymetazoline in 42 children with nasal symptoms such as nasal congestion. Akerlund et al (1989) assessed the nasal decongestant effect of oxymetazoline in the common cold.

**Graf et al. (1999)**

A parallel, randomized, double-blind trial, was carried out in which 35 patients with vasomotor rhinitis were randomized for treatment with oxymetazoline nasal spray either with (18 patients) or without (17 patients) benzalkonium chloride in the morning and in the evening for 10 days. Nasal mucosal swelling and nasal reactivity, as estimated by histamine challenge, were studied with rhinostereometry and acoustic rhinometry before and after treatment, and symptom scores of nasal stuffiness were estimated throughout the treatment. This study shows that rebound swelling does not follow 10 days’ use of oxymetazoline with or without benzalkonium chloride 3 times daily in patients with vasomotor rhinitis. However, this study indicates that benzalkonium chloride in nasal decongestant sprays affects the nasal mucosa also after short term use.

**Marantha et al. (1996)**

In a randomized and double-blind trial in 60 patients with common cold, 3 commercial nasal sprays were tested: benzydamine, xylometazoline combined with the secretolytic S-carboxymethylcysteine, and phenylephrine combined with the antihistaminic dimethindene maleate. The change in nasal patency was registered after 3 and 10 minutes and then after 2, 4, 6 and 8 hours. At the end, the patient gave a subjective evaluation of the used spray.

There was no change in nasal obstruction following application of NaCl or benzydamine. Xylometazoline/S-carboxymethylcysteine (+87%) or phenylephrine/dimethindene maleate (+113%) augmented nasal patency within minutes.

Using phenylephrine/dimethindene maleate the effect lasted less than 2 hours, while after xylometazoline/S-carboxymethylcysteine decongestion lasted more than 6 hours. The patients also subjectively reported an increase in nasal patency after the use of benzydamine and placebo,
although only phenylephrine/dimethindene maleate or xylometazoline/S-carboxymethylcysteine were judged good.

The effects on the nasal mucosa of a 1-month treatment with nasal sprays was investigated in a parallel, randomized, double-blind study performed in 30 healthy subjects. Ten subjects received oxymetazoline nasal spray, 10 subjects used a nasal spray containing the preservative benzalkonium chloride, and the others were treated with a placebo nasal spray. After 28 days of use, benzalkonium chloride spray alone induced an increase in nasal mucosal swelling. At the end of the month, the score for nasal stuffiness was significantly higher for the group treated with oxymetazoline than for those treated with benzalkonium chloride. Oxymetazoline nasal spray induced a pronounced increase in nasal reactivity, which was significantly greater than that induced in the placebo group. Long-term use of placebo and benzalkonium chloride nasal sprays also caused an increase in nasal reactivity, but not to the same extent as with the nasal sprays containing oxymetazoline.

In a randomised, double-blind, multicentered, verum-controlled tolerance study, a total of 307 patients with acute rhinitis were enrolled. The treatment with oxymetazoline with preservative, oxymetazoline without preservative and oxymetazoline with preservative was evaluated. When evaluated according to the parameters “feeling of dryness in nasal mucosa” and “burning sensation”, the Nasivin sanft 0.05% spray, which contains the active agent oxymetazoline without preservatives, proved to be considerably superior to preparations containing the preservative benzalkonium chloride. It was concluded that preparations without preservatives should be the preferred choice of treatment for acute rhinitis.

Hummel et al. (1998)
In a randomized, double-blind, placebo-controlled study, drug effects on olfactory function during the course of the spontaneously occurring cold were assessed. The investigation was performed in 36 subjects who received either placebo or oxymetazoline. Oxymetazoline clearly produced an increase in nasal volume.

Krempl and Noorily (1995)
Oxymetazoline has shown effective in records of 60 patients who presented to the emergency room with the diagnosis of epistaxis and who required medical management.

Lau et al. (1990)
In a randomized, double-blind, parallel clinical trial in 142 patients with perennial rhinitis, the efficiency of three treatments was evaluated: budesonide, terphenadine and budesonide plus oxymetazoline. After a treatment’s duration of 21 days, nasal symptoms were evaluated by the patients. Oxymetazoline together with budesonide, proved to be faster in relieving nasal blockage for the first three days than terphenadine.

IV.4 Clinical safety

The safety of oxymetazoline has been established a long time ago. The minimal effective dose is not known, neither for adults nor for children or elderly. Oxymetazoline is widely used in children and elderly. Children might be more vulnerable to side effects.

The most frequent adverse events of nasal oxymetazoline (> 1/100, < 1/10) are local minor events such as itching, irritation, dryness, or sneezing. When used at the recommended dose, topical oxymetazoline has virtually no systemic adverse effects (Passàli, 2006). In case of overdose some uncommon (> 1/10,000, < 1/1,000) adverse events can arise. These uncommon events are mainly related to stimulation of the cardiovascular or central nervous systems and include: increased arterial pressure and heart rate, palpitations, anxiety, nervousness, headache, tremor, and excessive sweating. Also sleep disorders, such as insomnia, may uncommonly occur (> 1/10,000, < 1/1,000) as a consequence of this hyper-reactivity of cerebral activity. The frequency of these sympathomimetic effects cannot be more accurately estimated from available data, but in any case they are very rare with oxymetazoline, and are virtually absent when avoiding prolonged or excessive use of the drug.
The duration of usage should be restricted, as one of the main possible adverse effects of nasal decongestants is the long-lasting mucosa alterations induced by the prolonged use of topical nasal decongestants, that may result in rhinitis medicamentosa (RM). RM incidence ranges from 1% to 9% and it is more common in young and middle-aged adults irrespective of the gender (Ramey et al, 2006). It is noted, however, that this is an adverse effect mainly associated with products containing sympathomimetic amines as ephedrine, whereas with oxymetazoline and other imidazoline derivatives, it is less relevant and less frequent. The exact pathophysiology of RM is unknown.

The label instruction not to use the product for longer than 7 days in a row and not to exceed the daily recommended dose should ensure that long term safety concerns are adequately addressed in the product information.

**Benzalkonium chloride**

Benzalkonium chloride (BKC) is the preservative of choice in a wide variety of prescription and over-the-counter aqueous nasal, ophthalmic and otic products. It has been in clinical use since 1935, and, according to the American College of Toxicology, BKC can be safely used as an antimicrobial agent at concentrations up to 0.1%. Oxymetazoline Focus nasal spray contains 0.02% BKC (around 25 mcg BKC/dose, or 50 mcg/day according to the maximum recommended dose in the SmPC), which is below the threshold for known adverse effects.

**IV.5 Risk Management Plan**

The MAH did not submit a Risk Management Plan. The safety profile of oxymetazoline containing medicinal products is well established and has maintained a positive benefit/risk ratio after many years of extensive patient exposure.

An RMP is not necessary for this medicinal product, as it was not required at the time of dossier submission. The MEB considers routine pharmacovigilance sufficient.

**IV.6 Discussion on the clinical aspects**

**Oxymetazoline 0.05% strength**

The Oxymetazoline HCl Focus nasal spray pump releases 0.07 ml in spray form, which means that 0.035 mg of oxymetazoline is administered in each instillation. Each instillation corresponds to 0.5 mg of oxymetazoline per ml (0.05%). Many trials published refer to the used strength of 0.05%. It has been demonstrated that this strength provides sufficient relief and has as a low adverse systemic effects rate.

**Pharmaceutical form**

The efficacy of oxymetazoline administered as a nasal spray has been shown in many controlled trials in patients with conditions such as nasal congestion, nasal hyperemia, rhinitis, common cold and epistaxis, as well as in healthy subjects. Especially in the publication by Slodki and Montgomery a major effectiveness of oxymetazoline spray compared to oxymetazoline drops was demonstrated.

The provided literature is considered sufficient to support that oxymetazoline HCl is well established in the local symptomatic relief of nasal congestion in adults and children aged 6 years and over. The efficacy and safety of oxymetazoline nasal spray are well known. The literature data can be bridged to the product of this application.

**V. USER CONSULTATION**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Oxymetazoline HCl 0.5 mg/ml Focus, nasal spray, solution has a proven chemical-pharmaceutical quality. The use of the active substance for local symptomatic relief of nasal congestion is considered well-established. Oxymetazoline HCl Focus nasal spray has a favourable efficacy and safety profile. Adequate non-clinical and clinical literature data have been provided.

The Board followed the advice of the assessors.

The MEB considered that well-established use has been demonstrated for this medicinal product and has therefore granted a marketing authorisation. Oxymetazoline HCl 0.5 mg/ml Focus, nasal spray, solution was authorised in the Netherlands on 19 January 2015.
Literature references


Lau SK, Wei WI, Van Hasselt CA, Sham CL, Woo J, Choa D. A clinical comparison of budesonide nasal aerosol, terfenadine and a combined therapy of budesonide and oxymetazoline in adult patients with perennial rhinitis. Asian Pacific journal of Allergy 1990;8:109-15


Slodki SJ, Montgomery CA. Clinical comparison of oxymetazoline and ephedrine in nasal decongestion. Current Therapeutic Research 1965; 7: 19-21

### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in the batch size (including batch size ranges) of the finished product; Submission of an updated Eur. certificate of suitability for the active substance.</td>
<td>IA/G</td>
<td>9-2-2015</td>
<td>24-2-2015</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use.</td>
<td>IA/G</td>
<td>15-6-2015</td>
<td>25-6-2015</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Submission of an updated Eur. certificate of suitability for the active substance.</td>
<td>IA</td>
<td>17-1-2017</td>
<td>22-1-2017</td>
<td>Approval</td>
<td>N</td>
</tr>
</tbody>
</table>