

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Afrin 0.5 mg/ml Neusspray oplossing, nasal spray solution
Afrin 0.5 mg/ml Neusspray oplossing met glycerol, nasal spray solution
Afrin 0.5 mg/ml Neusspray oplossing met kamille, nasal spray solution
Afrin 0.5 mg/ml Neusspray oplossing met menthol, nasal spray solution
Bayer B.V., the Netherlands

oxymetazoline (as 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/1971/001- 004/DC
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Pharmacotherapeutic group:	oxymetazoline
ATC code:	R01AA05
Route of administration:	nasal
Therapeutic indication:	Symptomatic relief of nasal congestion due to hay fever, common cold and sinusitis. Afrin is indicated in adults and children aged 6 years and over.
Prescription status:	non-prescription
Date of authorisation in NL:	8 August 2011
Concerned Member States:	Decentralised procedure with BG, CZ, EE, EL, HU, LT, LV, PL, PT, SI, and SK; repeat-use procedure with ES and RO
Application type/legal basis:	Directive 2001/83/EC, Article 10(a) well-established use

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), 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 Afrin 0.5 mg/ml Neusspray oplossing met glycerol/kamille/menthol (from here on "Afrin 0.5 mg/ml Neusspray, nasal spray solution), from Bayer B.V. The date of authorisation was on 8 August 2011 in the Netherlands.

The product is indicated for symptomatic relief of nasal congestion due to hay fever, common cold and sinusitis. Afrin is indicated in adults and children aged 6 years and over.

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

Oxymetazoline hydrochloride is a sympathomimetic agent which exerts a local vasoconstriction action in the nasal mucosa, reducing nasal congestion. Afrin Nasal Spray is described as a No-Drip formulation because it becomes more viscous when sprayed and remains on the mucosal membranes more effectively than a standard aqueous solution. Clinical studies have shown that oxymetazoline acts within a few minutes and its effect can last up to 12 hours following treatment.

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

This application concerns a bibliographical application based on well-established medicinal use of Afrin 0.5 mg/ml Neusspray. 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. *Medicinal use* does not exclusively mean *use as an authorised medicinal product*, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

The MAH has applied for regulatory advice in advance of this application. Two problems were discussed in particular:

- Was it possible for the MAH to use a reference product to support this application? Both the RMS and the MAH could not identify an oxymetazoline registration in the EU that could be considered a full dossier application which is also EU acquis. Therefore it was agreed that a generic application could not be submitted. Since oxymetazoline is extensively used for decades, a bibliographical application was accepted.
- The MAH proposed names for the medicinal products claiming additional efficacy due to the various flavouring excipients. This was considered not acceptable without additional data.

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

General information

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

Manufacture

The manufacturing process is covered by the CEP and therefore assessed by the EDQM.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. and the CEP. The specification is acceptable in view of the various European guidelines. Batch analytical data have been provided for 2 batches demonstrating compliance with the specification.

Stability of drug substance

The active substance is stable for 3 years when adequately stored. 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

Oxymetazoline HCL 0.5 mg/ml nasal spray contains as active substance per single dose (100 microlitre) 50 microgram xylometazoline hydrochloride. The nasal spray is packed a white, light-resistant, high-density polyethylene bottle sealed with a white polypropylene non pressurized pump assembly. The products are white to off-white, thick, gel-like suspensions.

The common excipients are: benzalkonium chloride, disodium edetate, sodium phosphate monobasic monohydrate, disodium phosphate anhydrous, povidone, benzalkoniumchloride, polyethyleneglycol, benzylalcohol, microcrystalline cellulose and carmellose sodium, and purified water.

Extra excipients for the original presentation: lemon flavour.

Extra excipients for the menthol presentation: propyleneglycol, cineole, camphor, levomenthol.

Extra excipients for the glycerol presentation: lemon flavour, glycerol.

Extra excipients for the chamomile presentation: glycerol, chamomile flavour.

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

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained.

Since the formulation contains antimicrobial preservatives 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 and benzyl alcohol in the concentration applied in the formulation (0.025% w/v each) obtained adequate preservative properties in the nasal solution. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The preparation of the solutions is a straight-forward process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 consecutive commercial-scale batches of all four formulations.

Control of excipients

The excipients comply with their Ph.Eur. requirements. These specifications are acceptable. For lemon and chamomile flavour adequate in-house specifications are provided.

Quality control of drug product

The product specification includes tests for appearance, identity (oxymetazoline HCl), assay (oxymetazoline HCl, benzyl alcohol, and benzalkonium chloride), pH, uniformity of mass, related substances (total impurities), and microbiological purity. The shelf-life requirements are expanded with tests for weight change, individual impurities, and a test for antimicrobial preservative effectiveness.

The analytical methods have been adequately described and validated. Batch analytical data of three production-scale batches of each drug flavour were tested, demonstrating compliance with the release specification.

Microbiological attributes

For the purpose of supporting marketing authorization in the EU, the Original formula product was evaluated according to the EP Preservative Challenge Test. The EP requirements are a reduction greater than 3 log for all time points for all bacteria and greater than 3 log reduction for all fungi at 14 days.

The product meets these acceptance criteria for bacteria and fungi.

Container closure system

The manufacturers statements of conformance of the plastic component and colorant used in the bottle and pump with Directive 2002/72/EC and Certificates of Analysis for the bottle and pump have been included.

Since dosing is defined by active ingredient concentration and number of sprays, the performance of the pump with the formulation was evaluated according to the EP <2.9.40>. The results demonstrated compliance with the Mass Uniformity requirements. Additionally a study of the dose volume (per actuation) and droplet size of the pump assembly was conducted. The study confirmed that the pump assembly delivers approximately 100 µL per actuation and that the pump assembly produces more droplets greater than 10 µm using the 'no drip' formulation as opposed to water. The droplets produced are expected to deposit predominantly in the nasal cavity.

Stability tests on the finished product

Stability data on the products has been provided on 6 production-scale batches divided by 1 or 2 batches of each flavour, stored at 25°C/40% RH (24 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. No out-of-specifications were observed. The proposed shelf-life of 2 years and the storage condition *Store below 25°C; Do not refrigerate or freeze*, can be granted.

In-use stability

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 30 days, as described in the SmPC as the maximum time after first use. The results showed no trends in the tested parameters.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Only glycerol is of ruminant animal origin (derived from tallow of animal). The vendor of the glycerol has been granted an EDQM TSE certificate. No other components of ruminant animal origin is 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 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 pre-clinical pharmacology, pharmacokinetics and toxicology. This overview is adequate.

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 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.

II.3 Clinical aspects

This application concerns a well-established use application, based on article Article 10(a) for Afrin nasal spray, an oxymetazoline HCl 0.5 mg/ml nasal spray. The excipients in Afrin nasal spray have been modified as compared with standard aqueous nasal spray products, to produce an aqueous solution that when sprayed becomes more viscous; hence, it is retained in the nasal cavity more than standard aqueous nasal spray products.

This application includes 4 variants of the no drip formulation: Afrin 0.5 mg/mL Nasal Spray, Afrin 0.5 mg/mL Nasal Spray with Menthol, Afrin 0.5 mg/mL Nasal Spray with Glycerol, Afrin 0.5 mg/mL Nasal Spray with Chamomile. These variants include a variety of aromatics or other inactive ingredients, all of which contain the same levels of oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties. The aromatic flavours and inactive ingredients are used in pharmaceutical products including nasal sprays. The indicated use for all four variants is the same: Symptomatic relief of nasal congestion due to hay fever, common cold and sinusitis.

Oxymetazoline hydrochloride (HCl) formulated in an aqueous nasal spray has been approved in 45 countries worldwide and marketed safely for more than 40 years. In Europe, the product obtained the first marketing authorization in Spain in 1965, and today several oxymetazoline HCl nasal products are marketed under various brand names such as Nasivin and Nasarox.

A limited number of clinical studies have been conducted with the formulation described in this submission to bridge this new product to the published literature data, all of which are based on the traditional oxymetazoline HCl aqueous solution. The studies with the formulas referenced in this submission were conducted to evaluate the tolerability, safety, comparative efficacy, and consumer acceptability of the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties.

II.3.1 Pharmacokinetics

Oxymetazoline HCl is considered a topical decongestant for relief of nasal congestion to be administered intranasally. Oxymetazoline HCl is a sympathomimetic agent that exerts a local vasoconstriction action at

the nasal mucosa to reduce nasal congestion. The therapeutic action of oxymetazoline HCl is thought to be due to stimulation of the peripheral α -adrenergic receptors of the vascular smooth muscles, which leads to vessel constriction, with little or no action on β -adrenergic receptors. Intranasal application of oxymetazoline HCl is thought to result in direct binding of α -adrenergic receptors in the nasal mucosa resulting in constriction of dilated arteries and reduction in nasal and sinus mucosal blood flow, which facilitates nasal passage breathing. The topical vasoconstriction effect of oxymetazoline HCl is rapid, resulting in nasal congestion relief within 5 minutes of administration and relief of nasal congestion can last up to 12 hours.

Non-clinical testing shows that absorption of oxymetazoline by either nasal or ocular routes is low (<10%). In man, plasma concentrations were too low to measure.

The oxymetazoline HCl 0.5 mg/mL nasal spray 'no drip' formula is considered by the MAH to be 'essentially similar' to oxymetazoline HCl 0.5 mg/mL nasal products in the EU since the concentration of the active and method of delivery to the nasal cavity is the same as that as specified in the Summary of Product Characteristics (SmPC) for oxymetazoline HCl containing nasal products marketed in the EU.

The major difference between the standard aqueous oxymetazoline HCl 0.5 mg/mL nasal sprays and the oxymetazoline HCl 0.5 mg/mL nasal spray 'no drip' formula is the addition of the excipients dispersible cellulose (microcrystalline cellulose and carmellose sodium EP) and povidone K29-32 EP as a rheology-modifying system, to provide the 'no drip' properties. Other inactive ingredient changes include the addition of aromatics or other inactive ingredients.

The microcrystalline cellulose/carmellose sodium in the oxymetazoline HCl 0.5 mg/mL nasal spray 'no drip' formula increases the viscosity of the liquid formulation in a resting state but under force exhibits reduced viscosity; thus, the nasal spray must be shaken to reduce viscosity so the formula can be sprayed. When sprayed into the nose, the nasal spray formula temporarily remains on the surface of the nasal mucosa, resulting in the 'no drip' sensation. Eventually, the product components are dispersed with mucus and expelled via the throat by the natural process of turbulent precipitation. Based on this natural physiological function the excipients in the formula are slowly expelled down the throat with mucus at about 1 cm per minute over a 5 to 10 minute period of time. Thus, the clearance of the product from the nose becomes a part of the natural nasal clearance process rather than noticeable "dripping" experience.

In conclusion 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. Different excipients are included in this oxymetazoline 'no drip' formulation which influence the viscosity of the formulation and affect the behaviour of the formulation in the nose; this means that they may affect the nasal absorption of oxymetazoline. Therefore, the MAH has not demonstrated that the excipients do not affect the nasal absorption of oxymetazoline, and thus may affect the safety and consequently the benefit-risk established for oxymetazoline nasal spray 0.5 mg/ml.

II.3.2 Clinical efficacy

II.3.2.1 Introduction

The efficacy of intranasal oxymetazoline HCl is well-established based on the extensive number of clinical study publications. In order to demonstrate efficacy and safety of oxymetazoline HCl a review of the published studies on oxymetazoline HCl as well as, unpublished clinical studies on oxymetazoline HCl and new studies on the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties were submitted.

II.3.2.2 Efficacy

Review of studies with xylomethazoline from literature is given, with reports dating from 1965-2005. Additionally unpublished data from clinical study (Study 93-02) have been submitted to support 12 hour efficacy of oxymetazoline HCl 0.5 mg/mL nasal spray. Two other studies, study PE98-74 and study PE99-01, were performed to investigate consumer acceptability of the new formulation.

Study 93-02 was a seven-day dose-ranging study on oxymetazoline HCl nasal spray primarily to evaluate rebound effect in adult subjects over 18 years of age with nasal congestion. The primary objective was to evaluate rebound with repeated dosing over seven days. Subjects also rated the ability of an oxymetazoline HCl nasal spray to provide relief from nasal congestion at various times after dosing. One

hundred thirty-eight (138) subjects completed the study and were assigned to one of 5 test groups: saline control (two, 100 µL sprays per nostril), 0.025% oxymetazoline HCl (one 50 µL spray per nostril), 0.025% oxymetazoline HCl (one, 100 µL spray per nostril), 0.05% oxymetazoline HCl (two, 50 µL sprays per nostril), or 0.05% oxymetazoline HCl (two, 100 µL sprays per nostril). Only efficacy of the 0.05% oxymetazoline HCl and saline control nasal spray data is presented because the 0.05% level of oxymetazoline HCl is the approved and widely used level of active in nasal sprays in the EU and the level of active in the oxymetazoline HCl nasal spray 'no drip' formula in this submission.

At the beginning of Study 93-02 before testing any nasal spray, subjects rated their degree of nasal congestion using a 10 cm visual analogue scale, by making a 'tic-mark' on the scale in a location that best represented the degree of nasal congestion they were experiencing. The two anchors on either end of the visual analogue scale (VAS) were "completely clear" (a score of 0) and "completely blocked" (a score of 100). In general, nasal symptoms such as rhinorrhoea and blocked nose are scored in these agents. In trials with this type of agents primary measures of efficacy are patient self-rated symptom scores. Symptom scores should be collected at baseline and daily over the course of the trial.

Subjects rated their nasal congestion in both nostrils, and then rated the blockage in each nostril individually by closing the opposite nostril with their finger. Each subject then used a 0.05% oxymetazoline HCl nasal spray and rated their degree of nasal congestion at one hour, 8 to 10 hours, and 12 hours after using the nasal spray. One group of subjects tested the nasal spray using a 50 µL metered dose pump, and one group tested the nasal spray using a 100 µL metered dose pump. Subjects testing the 0.05% oxymetazoline HCl or the saline nasal sprays were instructed to deliver two sprays per nostril.

Table 1 shows nasal congestion scores calculated from the visual analogue scale. Baseline nasal congestion scores before initial use were similar for both oxymetazoline HCl spray groups and the saline nasal spray control group. Nasal congestion scores decreased significantly 1 hour after first use of the oxymetazoline HCl nasal sprays, indicating significant relief (data not shown). Twelve hours after first use, nasal congestion scores were still significantly lower than baseline for both oxymetazoline HCl spray groups, but scores began to return to baseline. Nasal congestion scores for the saline control group showed no difference between the baseline and 12-hour congestion scores.

Table 1 Study 93-02, Nasal Congestion Scores Before and 12 Hours after Oxymetazoline HCl Nasal Spray Use*

Nasal Spray Sample	Baseline congestion before initial use	Congestion 12 hours after first use	p-value vs. baseline†
0.05% oxymetazoline HCl (50 µL spray dose)	57.1± 15.4 (n=25)	43.7± 26.4 (n=25)	P = 0.011
0.05% oxymetazoline HCl (100 µL spray dose)	53.2± 12.8 (n=29)	42.6± 24.1 (n=29)	P = 0.008
Saline control (100 µL spray dose)	53.3± 15.3 (n=28)	50.0± 22.3 (n=28)	P = 0.42

*Study 93-02. All subjects testing 0.05% oxymetazoline hydrochloride nasal spray were instructed to deliver two spray doses to each nostril. Nasal congestion scores are presented for both nostrils after the first use on day 1. Scores were calculated from the visual analogue scale where 0=completely clear and 100=completely blocked.

† Statistical analysis completed using paired t-test. Statistical significance detected when p<0.05.

Based on these data the MAH states that a 0.05% oxymetazoline HCl nasal spray can provide significant congestion relief 12 hours after use, compared to baseline. Additionally, twice daily dosing of the nasal spray is stated to be demonstrated since each dose provided relief of nasal congestion till 12 hours.

Furthermore clinical studies were submitted in order to support the tolerability of the new formulation of oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties. Two unpublished studies (Studies PE98-74 and PE99-01) were conducted to evaluate the tolerability and consumer acceptability of the

oxymetazoline HCl 0.5 mg/mL nasal spray 'no drip' formula. These studies evaluated several nasal spray formulations, including the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties. The studies were conducted to evaluate the clinical acceptability of the oxymetazoline HCl 0.5 mg/mL nasal spray 'no drip' formula.

Study PE98-74 was a pilot study to evaluate product acceptability of three oxymetazoline HCl prototype formulas compared to currently USA marketed original Afrin Nasal Spray in 50 adults with at least mild nasal congestion. One of the prototype formulas was the proposed EU commercial oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties.

The objective of the pilot study was to evaluate the prototype nasal spray (N65-012) for their ability to reduce and/or eliminate the sensation of product dripping out of the nose compared to the original oxymetazoline HCl nasal spray (currently USA marketed as Afrin Nasal Spray, H69-100)). Secondly, the formulas were evaluated for onset of noticeable congestion relief, bridging and confirming the expected performance of oxymetazoline HCl 0.5 mg/mL. Forty-nine subjects with at least mild, self-perceived nasal congestion evaluated the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties in the paired-comparison study.

Subjects were asked to indicate if they felt the product dripping up to 1 minute after use and indicate when they experienced noticeable congestion relief after use. More subjects reported absence of dripping with the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties (whether actual dripping or perception of dripping) compared to the original oxymetazoline HCl nasal spray. The mean onset of noticeable congestion relief was not statistically significant different between the oxymetazoline HCl 0.5 mg/ml nasal spray formula with 'no drip' properties and the original oxymetazoline HCl nasal spray (Table 3 and Table 4) indicating a similar therapeutic response. The MAH states that these results indicate that the new oxymetazoline HCl 0.5 mg/mL nasal spray formula can reduce the sensation of dripping and yet maintain the same expected rapid onset of action of the active ingredient.

Table 3 Study PE98-74, Percentage of Subjects Reporting Absence of Dripping from Nose

	Total % (n=number of uses)*
Formula H69-100, Original Oxymetazoline HCl 0.5mg/mL Nasal Spray	43% (n=138)
Formula N65-012, Oxymetazoline HCl 0.5mg/mL Nasal Spray, with 'no drip' properties	66% (n=49)

*Note: each subject tested the original nasal spray each time they tested one of the three prototype nasal spray; thus, there were more uses of the original nasal spray than the nasal spray with 'no drip' properties.

Table 4 Study PE98-74, Onset of Noticeable Congestion Relief

Formula Tested	N* (number of uses)	Minimum Onset of Action (seconds)	Maximum Onset of Action (seconds)	Mean	Standard Deviation
Formula H69-100 Original Oxymetazoline HCl 0.5mg/mL Nasal Spray	136	5	290	58.9	48.8
Formula N65-012, Oxymetazoline HCl 0.5mg/mL Nasal Spray, with 'no drip' properties	49	5	124	43.8	25.4

N*= number of uses (due to paired comparison test design, original nasal spray was tested with each of the three prototype nasal sprays; the number of subjects testing N65-012 was 49). Minimum=earliest time point in seconds that noticeable congestion relief was reported. Maximum=longest time point in seconds that noticeable congestion relief was reported.

Study PE99-01 was a clinical consumer use study to evaluate the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties to evaluate consumer perception of the 'no drip' formula attributes. One hundred and one (101) adult subjects with self-perceived nasal congestion due to allergies or common cold were recruited to participate in this study. Subjects had to experience at least mild self-perceived congestion overall for both nostrils before testing the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties. Subjects tested the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties according to label instructions. One minute after use, subjects completed a study questionnaire. Subjects were asked to rate their agreement or disagreement with several statements regarding their perceptions after use including the statement "the product stayed in my nose" using a 5 point balanced scale from strongly agree to strongly disagree. Results in Table 5 below show that overall, 95% of all subjects agreed that the product stayed in their nose after use. The overall agreement scores represented a sum of scores for strongly agree (68.3%) and somewhat agree (26.7%).

The oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties has been shown in clinical testing to have the same expected onset of action as regular Afrin Nasal Spray with oxymetazoline HCl 0.5 mg/mL and could be effective at relieving nasal congestion rapidly with relief lasting up to 12 hours. According to the MAH the excipients were considered to have no effect on the efficacy of oxymetazoline HCl based on the comparative clinical testing in study PE 98-74 showing a similar expected onset of action between the Afrin Nasal Spray and Afrin No Drip Nasal Spray.

Table 5 Study PE99-01, Subjective Responses Regarding Acceptability of Nasal Spray 1 Minute After Use*

Response Option	Number and % of subjects selecting the response
Strongly Agree	69 (68.3%)
Somewhat Agree	27 (26.7%)
Neither Agree nor Disagree	1 (1%)
Somewhat Disagree	4 (4%)
Strongly Disagree	0 (0%)

*One minute after use, all subjects were asked the following question: Using the scale, please rate your agreement or disagreement with the following statement after using the nasal spray product: "the product stayed in my nose"

II.3.2.3 Conclusion

Due to the similar onset of action, the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties might be similarly bioavailable as the regular oxymetazoline HCl nasal spray without 'no drip' properties although the submitted data are limited. Xylometazoline has been extensively used and its efficacy has been generally accepted. This application is made in accordance with Article 10(a), which refers to the well-established use of oxymetazoline HCl nasal spray 0.5 mg/ml. Based on additional new clinical data provided by the MAH, efficacy has been demonstrated. The claimed advantage of this viscous formulation that it is retained in the nasal cavity more than standard aqueous nasal spray products and results in 'no drip' has sufficiently been proven. Afrin® might relieve nasal congestion lasting up to 12 hours.

II.3.3 Clinical Safety

Four unpublished studies were conducted to evaluate the oxymetazoline HCl 0.5 mg/mL formula with 'no drip' properties. A total of 191 subjects received at least one dose of 'no drip' nasal spray of which 10 subjects received 'no drip' nasal spray without lemon; 42 subjects received doses for three days. Study HT000001 and Study 999203 are safety and tolerability studies. Safety data collected in Study 93-02, as well as in two other unpublished studies are described for the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties.

In clinical Study 93-02: 31 adverse events occurred which were considered possibly product related. These all resolved during the study and did not require medical intervention. These adverse events

ranged from headaches, lightheadedness, and nervousness to increased congestion, burning of nostrils, and nasal discharges. Two adverse events resulted in discontinuation from the study. No serious adverse events were reported. The MAH concluded that: *“Day 8 congestion scores do not rise above Day 7 baseline or 12 hour scores, indicating patients do not experience rebound effects.”*

Study HT000001 and 999203 evaluated several nasal spray formulations, including the proposed EU ‘no drip’ formulation

The most common symptoms related to the local effect of the nasal spray and consisted of burning or stinging sensations of the nostrils. Other adverse events could be related to the underlying symptoms for which treatment was being used (colds, allergies etc).

Study 999203 evaluated and compared the effect of three oxymetazoline HCl 0.5 mg/mL nasal sprays on the appearance of and secretions from the nasal cavity. The objective of the study was to evaluate and compare the effect of a control nasal spray with oxymetazoline HCl 0.5 mg/mL and two new nasal sprays, one being the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties. Twenty (20) adults suffering from mild nasal congestion participated in the study. Subjects administered the control nasal spray in one nostril and one of the new nasal sprays in the other nostril. Clinical evaluations were made before nasal spray use and then after 3 days of twice daily dosing with each nasal spray. Clinical evaluations included the severity of secretions, quantity and consistency of colour; presence of ulceration, polyps, and blood; normalcy of the septum, and size and colour of turbinates. Six subjects reported a total of 12 adverse events. Three of these subjects reported a total of 6 adverse events that were possibly or probably related to product use. Three subjects had adverse events unrelated to product use, and there were no serious adverse events reported.

Two subjects reported mild adverse events associated with use of the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties: one subject reported 2 episodes of mild-slight stinging for 2 seconds in the right nostril and lacrimation of the right eye once for 2 seconds and one subject reported stinging in the nostril after use. No increased inflammation or irritation (based on the size and colour of turbinates) was observed for the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties in this study.

Study HT000001 was conducted to evaluate the safety and tolerability of the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties that also contained aromatic flavours. The study evaluated and compared the effect of two nasal sprays, a control nasal spray and the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties on the appearance of and secretions from the nasal cavity. Twenty-two adults suffering from mild nasal congestion participated in the study. Clinical evaluations were made before nasal spray use and then after 3 days of twice daily dosing with each nasal spray. Clinical evaluations included the severity of secretions, quantity and consistency of colour; presence of ulceration, polyps, and blood; normalcy of the septum, and size and colour of turbinates. Eight adverse events were reported by three subjects; one was possibly related to the test article. Seven subjects reported subjective symptoms related to test article usage and have been included to provide a full listing of responses to treatment. No clinically significant effects on the appearance of the nasal cavity or nasal secretions were observed with either nasal spray.

Results from Study 999203 show that the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties has comparable safety and tolerability to a nasal spray without 'no drip' properties, supporting the safety of the excipients that provide the ‘no drip’ properties. In addition, the nasal spray safety and tolerability was comparable with or without lemon flavour. Results from Study HT000001 show that the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties containing menthol aromatic flavours has comparable safety and tolerability to an aromatic nasal spray without the 'no drip' properties. However, the oxymetazoline was only used very shortly in these studies.

To maintain microbiological safety, the nasal spray contains 0.025% equivalent concentration of benzalkonium chloride as a preservative. The MAH refers to several reports in the scientific literature that have evaluated the safety of intranasal benzalkonium chloride in both healthy patients and those with rhinitis. There is some discussion about the safety of benzalkonium chloride in the literature, although a recent safety review of the 18 preclinical and clinical studies evaluating short and long term intranasal exposure of benzalkonium chloride indicates that this preservative is safe and well tolerated for both long

and short term clinical use (Marple *et al* 2004¹). Few clinical studies evaluating safety of 0.1% benzalkonium chloride in an oxymetazoline nasal spray suggest that exaggerated use (3 times daily use for 30 days) may cause rhinitis medicamentosa (rebound congestion) (Graf and Hallen, 1996²). Published clinical studies show that when used according to label instructions (no longer than one week), oxymetazoline nasal sprays with benzalkonium chloride do not cause damage to the nasal epithelia and do not induce rebound congestion (Graf *et al*, 1999³, Inanli *et al*, 2002⁴, Yoo *et al*, 1997⁵; Watanabe *et al*, 2003⁶).

In conclusion 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 label.

II.4 Benefit / Risk assessment

Intranasal products containing oxymetazoline HCl 0.5 mg/mL are used in the treatment of nasal stuffiness or sinus congestion in such conditions as the common cold, hay fever, allergies or sinusitis, and have been available world wide for many years as an aqueous nasal spray. Based on previous literature and extended use these products have been accepted in providing rapid onset of action and each dose can provide up to 12 hours of relief from nasal congestion.

Benzalkonium chloride could adversely affect the safety profile of this nasal spray, when used according to recommended label instructions. Symptoms of common colds and hay fever often occur frequently and might lead to repeating use of decongestants such as Afrin®. Therefore the MAH committed to submit PSURs at a yearly period for the first number of years. A clear distinction between aqueous and viscous formulation must be discussed in the PSURs.

II.5 Conclusion on Clinical Efficacy and Safety

The data presented in the report demonstrate the tolerability, safety, and efficacy of the oxymetazoline HCl 0.5 mg/mL nasal spray with 'no drip' properties.

This formulation of oxymetazoline has different properties than the already marketed formulation and therefore a clear clinical comparison is not possible.

The benefit/risk of Afrin®, oxymetazoline nasal spray, for over-the-counter treatment of nasal stuffiness or sinus congestion in such conditions as the common cold, hay fever, allergies or sinusitis, is positive. The MAH committed to confirm with post marketing data that the safety of this medicinal product is comparable with already registered oxymetazoline hydrochloride formulas in the EU.

Risk management plan

¹ **Marple B**, Roland P, Benninger M. 2004. Safety review of benzalkonium chloride used as a preservative in intranasal solutions: An overview of conflicting data and opinions. *Otolaryngology– Head and Neck Surgery* 130(1): 131- 141.

² **Graf P**, Hallén H. 1996. Effect on the Nasal Mucosa of Long-Term Treatment With Oxymetazoline, Benzalkonium Chloride, and Placebo Nasal Sprays. *Laryngoscope*, 106:605-609.

³ **Graf P**, Enerdal J, Hallen H. 1999. Ten days use of Oxymetazoline nasal spray with or without benzalkonium chloride in patients with vasomotor rhinitis. *Archives of Otolaryngology and Head Neck Surgery*, 125(10): 1128-1132.

⁴ **Inanli S**, Ozturk O, Korkmaz M, Tutkun A, Batman C. 2002. The effects of topical agents of fluticasone propionate, oxymetazoline, and 3% and 0.9% sodium chloride solutions on mucociliary clearance in the therapy of acute bacterial rhinosinusitis *in vivo*. *Laryngoscope*; 112(2):320–5.

⁵ **Yoo JK**, Seikaly H, Calhoun KH. 1997. Extended use of topical nasal decongestants. *Laryngoscope* 107: 40-43.

⁶ **Watanabe H**. 2003. Oxymetazoline nasal spray three times daily for four weeks in normal subjects is not associated with rebound congestion or tachyphylaxis. *Rhinology* 41, no. 3: 167–74.

Oxymetazoline was first approved in 1965, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of oxymetazoline 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 SmPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

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 English package leaflet was tested with English native speakers. It was noted that a lot of questions implied that the medicinal product could have been prescribed. Particular for an OTC product the questions should have been directed to self diagnosis. It was noted that some of the interviewees mentioned that the PL contained difficult terms. No endeavour has been seen that something was done with these observations. Especially for an OTC product readability is important.

During the procedure the MAH sufficiently improved the PL and the issues were considered to be resolved.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Afrin 0.5 mg/ml Neusspray oplossing met glycerol/kamille/menthol, nasal spray have a proven chemical-pharmaceutical quality. With the MAA for oxymetazoline hydrochloride the MAH has submitted a dossier compliant with a bibliographical application. Although the benefit risk for oxymetazoline is well known, considering the several decades of experience with oxymetazoline, the member states consider that the Afrin formulation needs more bridging data. During this procedure additional data was generated to show ensuring comparability with aqueous formulations already registered in the EU.

Therefore, the benefit/risk of Afrin oxymetazoline nasal spray, for over-the-counter treatment of nasal stuffiness or sinus congestion in such conditions as the common cold, hay fever, allergies or sinusitis, is positive. However, the MAH committed to submit additional post-marketing data to show that safety of this medicinal product is comparable with already registered oxymetazoline hydrochloride formulas in the EU through yearly PSURs for an unknown period.

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

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The SmPC, package leaflet and labelling are in the agreed templates.

The products were discussed In the Board meeting of 27 January 2011. The Board followed the advice of the assessors. Afrin 0.5 mg/ml Neusspray oplossing met glycerol/kamille/menthol, nasal spray was authorised in the Netherlands on 8 August 2011, under the condition that the MAH will show post-marketing that safety of this medicinal product is comparable with already registered oxymetazoline hydrochloride formulas in the EU.

The PSUR submission cycle is yearly harmonised with the DLP August 2010 which means that the first PSUR must be submitted not later than 60 days after 31 August 2012 with a PSUR period: 29 August 2011 – 28 August 2012.

A clear distinction between aqueous and viscous formula has to be discussed in the PSURs.

The date for the first renewal will be 30 April 2015.

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

- A yearly PSUR will be submitted for oxymetazoline marketed by the MAH for an unknown amount of years (The number of years will depend on the assessment of the PSURs.)
- In the PSURs a clear distinction must be made between reports obtained for Afrin and aqueous formulas.

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
RMP	Risk Management Plan
RMS	Reference Member State
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	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
Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH.	NL/H/1971/001-004/IA/001	IA	19-3-2012	18-4-2012	Approval	N
Change in batch release site.	NL/H/1971/001-004/IA/002	IA	19-7-2012	26-7-2012	Approval	N
Repeat-use procedure with Spain and Romania.	NL/H/1971/001-004/E/001	Repeat Use	4-9-2012	3-12-2012	Approval	Y, Annex I
Name change of the MAH in Greece.	NL/H/1971/001-004/IA/003	IA	16-7-2012	15-8-2012	Approval	N
Introduction of the summary of Pharmacovigilance System.	NL/H/1971/001-004/IA/004/G	IA/G	12-2-2013	14-3-2013	Approval	N
Address change of the MAH in Portugal.	NL/H/1971/001-004/IA/005	IA	4-3-2013	3-4-2013	Approval	N
Change in the name and/or address of a manufacturer/importer of the finished product.	NL/H/1971/001-004/IA/006/G	IA/G	3-4-2013	3-5-2013	Approval	N
Change in the (invented) name of the medicinal product in Portugal.	NL/H/1971/001-004/IB/007	IB	15-3-2013	15-4-2013	Approval	N
Change in the (invented) name of the medicinal product in Spain.	NL/H/1971/001-004/IB/008	IB	11-9-2013	11-11-2013	Approval	N
Update of the summary of the PSMF and change in QPPV.	NL/H/1971/001-004/IA/009/G	IA/G	8-12-2013	7-1-2014	Approval	N
Renewal of the marketing authorisation.	NL/H/1971/001-004/R/001	Renewal	17-11-2014	29-4-2015	Approval	Y, Annex II

Annex I – Repeat-use procedure (NL/H/1971/001-004/E/001)

The repeat-use procedure was started on 4 September 2012, with two concerned member states: Spain and Romania. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states mutually recognised the RMS's assessment, and have therefore granted a marketing authorisation. The repeat-use procedure was finished on 3 December 2012.

The date for the first renewal is: 30 April 2015.

No new post-approval commitments were made during the procedure repeat-use procedure.

Annex II – Renewal of the marketing authorisation (NL/H/1971/001-004/R/001)

I RECOMMENDATION

Based on the review of the data submitted for the renewal application, the member states consider that the benefit/risk balance of *Afrin 0.5 mg/ml Neusspray oplossing met glycerol/kamille/menthol* is positive. A renewal with unlimited validity was granted.

II SCIENTIFIC DISCUSSION

II.1 Introduction

The registered Afrin 0.5 mg/ml nasal spray solution, also the formulas that contain menthol, glycerol and chamomile, is indicated for symptomatic relief of nasal congestion due to hay fever, common cold and sinusitis in adults and children aged 6 years and older.

The product is registered according to Article 10a, well-established use, of Directive 2001/83/EC.

The first marketing authorization for Afrin 0.5 mg/ml nasal spray solution was obtained on 8 August 2011 in the Netherlands.

Following approval of Afrin formula No Drip solution, the MAH made a commitment to provide yearly distinctive evaluation of the post-marketing data between the aqueous formulas and the newly approved Afrin formula No Drip solution. The latest reviewed PSUR for this evaluation covered the period of 29 August 2012 to 28 August 2013. The following was concluded:

- drug administration/medication error should be closely monitored
- drug ineffectiveness and related MedDRA terms for Afrin No drip and Afrin Plain Nasal formulations should be closely monitored

As part of this renewal the MAH submitted:

- an addendum to the clinical overview covering the period of 08 August 2011 to 22 April 2014.
- an expert statement covering the period August 2011 to April 2014.

II.2 GMP compliance statements

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance

Regarding GMP for the active substance a statement is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

II.3 Quality

In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure a quality expert statement has been submitted for Afrin confirming:

- That the products are in compliance with the requirements of Directive 2001/83/EC which obliges the MAH to take account of technical and scientific progress and introduce any changes.
- That all changes relating to the quality of the products have been made following applications for variations and that the product conforms to the current CHMP quality guidelines.
- The currently authorised specifications for the active substance and the finished products with the qualitative and quantitative composition have been provided.

There are no outstanding quality commitments.

II.4 Clinical aspects

II.4.1 Clinical efficacy

No new clinical data on efficacy have become available during this review period.

II.4.2 Clinical safety

The International Birth Date (IBD) for oxymetazoline hydrochloride is 4 December 1963 and was first approved in Australia. In the EU, the first marketing authorization for Afrin oxymetazoline was obtained on 8 August 2011 in the Netherlands. At the time of the renewal oxymetazoline hydrochloride is approved in 51 countries under various trade names.

The number of patients exposed to the product is estimated about 126,819,655 patient years for renewal period and 493,917,473 patient years cumulatively, based on worldwide sales figures of the MAH and an average daily dose of 8 sprays (drops) per day for 7 days.

The MAH provided all serious and non-serious adverse events (AE) reported post-marketing for the nasal formulations. Cumulatively between August 2011 and April 2014, a total of 2,224 adverse events (49 serious and 2,175 non-serious) were received by the MAH. Most frequently reported serious adverse events (SAE) were myocardial infarction (n=3), epistaxis (n=3), swelling face (n=2), drug dependence (n=2), and increased blood pressure (n=2). All other SAEs were reported only once.

Most non-serious AEs were reported under the system-organ class general disorders (n=690), with 'drug ineffective' (n=212) as most reported AE, and under respiratory disorders (n=438), with 'nasal discomfort' (n=134) as most reported AE.

Following PSUR assessment, the MAH committed to give a separate comparison of frequency and nature of AEs between no drip and nasal formulations. This should be provided in the next PSUR.

Overall, from the reported (S)AEs in the current renewal period, no new safety issues were identified. Taking into account the estimated patient exposure, the number of serious adverse events is low. The current SmPC is considered to sufficiently reflect the reported safety profile and therefore no regulatory action is required.

As already requested, the MAH should closely monitor 'drug ineffectiveness' and return to this topic in the next PSUR.

During the period under review, one clinical trial was completed. In Study PT13-01 Afrin No Drip Original Nasal Pump Mist was used as a comparator to Reformulated Nasal Pump Mist. This was a single application of the respective products using 2-3 pumps in each nostril. At 1 minute time point after product use, 98 subjects (88.3%) rated their experience with the Afrin No Drip Original Nasal Pump Mist as comfortable (extremely, moderately or slightly) and 8 subjects (7.2%) rated their experience as uncomfortable (slightly or moderate). At the 5 minute time point after product use 103 subjects (92.8%) indicated that they did not experience any stinging or burning sensations associated with the use of the test products. No non-serious or serious adverse events were observed or reported by subjects during the

course of this study.

There have been no clinical studies initiated, ongoing or finalized by the MAH during the period covered by this renewal. A review on literature revealed no new safety information.

The MAH included the following safety concerns in the RMP:

<p>Important identified/potential risks</p>	<ul style="list-style-type: none"> • Rebound Congestion • Exacerbation of heart disease • Exacerbation of high blood pressure • Exacerbation of thyroid disease • Exacerbation of diabetes • Exacerbation of difficulty in urination due to enlargement of the prostate gland • Use in patients with sensitivity to sympathomimetic agents • Use in patients taking or who have taken MAOIs taken in previous 2 weeks • Use in patients with transsphenoidal hypophysectomy • Use in patients with acute coronary disease or cardiac asthma • Use in patients with rhinitis sicca
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In future PSURs, the MAH should present the safety concerns separately for identified and potential risks. Lack of information regarding safety of use in certain patient groups should be covered under “missing information”. In line with the safety specification laid down for a xylometazoline product, it is requested to add as important potential risks ‘misuse’, ‘overdose’, ‘long term use (more than 7 days)’ and ‘lack of efficacy in children aged 6-12 years’.

As concluded in the PSUR, covering the period of 29 August 2012 to 28 August 2013, the MAH is requested to closely monitor the following:

- drug administration/medication error
- drug ineffectiveness and related MedDRA terms for Afrin No drip and Afrin Plain Nasal formulations

II.5 Product information

During the period covered by this renewal, no safety related changes to the SmPC have been performed. The SmPC, package leaflet and labelling have been updated in line with the most recent QRD template, this is acceptable.

II.6 Outstanding commitments

The following post-approval commitments are still outstanding:

Pharmacovigilance

In the next PSUR:

- drug administration/medication error should be closely monitored
- drug ineffectiveness and related MedDRA terms for Afrin No drip and Afrin Plain Nasal formulations should be closely monitored
- a separate comparison of frequency and nature of AEs between no drip and nasal formulations should be given
- the MAH should present the safety concerns separately for identified and potential risks
- the MAH is requested to add as important potential risks ‘misuse’, ‘overdose’, ‘long term use (more than 7 days)’ and ‘lack of efficacy in children aged 6-12 years’

The MAH should continue to submit PSURs in accordance with the EURD list.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

No new clinical data have become available that changed the benefit risk assessment. The assessment of the submitted data did not reveal new safety concerns. The follow-up measures listed above should be addressed in the next PSUR.

The RMS is of the opinion that the renewal can be granted with unlimited validity. The renewal procedure ended positively on 29 April 2015. The common renewal date is set on 30 April 2015.