20 November 2014
EMA/37163/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pursuant to Article 30 of Directive 2001/83/EC

Nasonex and associated names

INN of the active substance: Mometasone furoate

Marketing authorisation holder: Merck sharp & Dohme BV group of companies and associated companies

Procedure no: EMEA/H/A-30/1374

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 17 September 2013 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics (SmPC), labelling and package leaflet of the medicinal products:

Nasonex and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the September 2013 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Dr Kristina Dunder as rapporteur and Dr David Lyons as co-rapporteur.

The product is currently authorised according to the national procedure in 16 European countries (Bulgaria, Czech Republic, Estonia, France, Hungary, Iceland, Lithuania, Latvia, Malta, Norway, Poland, Romania, Sweden, Slovenia, Slovakia and Croatia).

Nasonex Nasal Spray is also authorised according to the mutual recognition procedure (MRP) since April 1997, in the following European Member States; United Kingdom (reference Member State (RMS)), Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, Ireland, Italy, Luxembourg, Netherlands, and Portugal.

In addition, in Cyprus Nasonex is registered under Article 126a of Directive 2001/83/EC, which allows a country to place a product on the market for justified public health reasons, in the absence of a marketing authorisation or of a pending application.

Due to the divergent national decisions taken by Member States concerning the authorisation of Nasonex and associated names, the European Commission (EC) notified the European Medicines Agency of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the authorised SmPCs for the above-mentioned product, and thus to harmonise the SmPCs across the EU.

2. Scientific discussion during the referral procedure

2.1. Introduction

Nasonex Nasal Spray 50 µg is a metered-dose, manual pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate, in an aqueous medium containing glycerine, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, citric acid, benzalkonium chloride, and polysorbate 80.

The active ingredient of Nasonex - mometasone furoate monohydrate, is a synthetic, 17-heterocyclic corticosteroid with anti-inflammatory activity and with less potential to cause systemic side effects often associated with the use of corticosteroids (e.g., hypothalamic pituitary-adrenal [HPA]-axis suppression).

2.2. Critical Evaluation

As the current MRP product information (PI) is already approved in 13 Members States, and the available efficacy and safety data supports the current MRP PI, the MAH has proposed the MRP PI as the basis for the harmonized PI for all Member States.

Section 4.1 – Therapeutic Indications

Rhinitis

Treatment of symptoms of rhinitis

All concerned Member States have approved the indication for the treatment of symptoms of rhinitis in children and adults since 1990.

Nineteen Phase II and III studies have been completed using mometasone furoate in adolescents and adults in the treatment and prophylaxis of seasonal allergic rhinitis and treatment of perennial rhinitis.

- Seasonal allergic rhinitis

Six studies were conducted to demonstrate the efficacy of mometasone furoate in 2544 patients with seasonal allergic rhinitis randomised to treatment with mometasone furoate, placebo or active control. Of the six studies, four were pooled, and the patient diary results showed a reduction from baseline of 33% compared to 15% in placebo-treated patients in the first two weeks of treatment with mometasone furoate. The mean scores for physician evaluations of total nasal symptoms showed greater reductions for mometasone furoate at all visits (ranging from 36 to 62%) compared to placebo (22% to 48%).

- Perennial rhinitis

Nine studies were conducted to assess the efficacy of perennial rhinitis, including a total of 3159 patients. Of the nine studies, four studies in perennial rhinitis were double-blind and placebo-controlled, and two studies included subjects with perennial non-allergic rhinitis (PNAR). A total of nine subjects with PNAR were included in these two studies.

The results from the four pooled double-blind, placebo-controlled studies in perennial rhinitis, showed that total nasal symptom scores recorded in patient diaries were almost identical in the morning vs evening, supporting the efficacy of mometasone furoate when dosed once daily.

Based on the nine studies in the original perennial rhinitis program, the perennial rhinitis indication was approved for the MRP countries in 1997 with the UK acting as reference member state (RMS), and by the other concerned Member States between 1997 and 1998. Subsequently, a study Q97-921 specifically in subjects with PNAR was completed indicating a positive outcome, and resulting in an indication for PNAR being granted in May 2000 in Sweden.

These studies support the proposed indication for the symptomatic treatment of rhinitis (seasonal allergic and perennial) in adults.

Paediatric population

In six Member States the age range of 3-11 years has been approved whereas the remaining Member States (including the MRP countries) have approved 6 years as the lowest age of treatment of rhinitis.

The MAH has provided information on the paediatric program and the efficacy and safety study results for this subpopulation in order to clarify the age range for the harmonised PI. In particular, the data on

children ages 3 to 5 years included in the paediatric program were further examined as shown in the table below.

Mometasone Furoate Nasal Spray Pediatric Program (Ages 2 to 11 Years)
Studies Including Children Ages 3 to 5 Years

Study No.	Phase	Study Type	Treatment Duration	Age Range (years)	Indication	Total No. Randomized	No. Randomized (Total Daily Dose): Ages 3 to 5 Years
C95-136	I	Safety: HPA axis	14 days	3 to 5	Allergic rhinitis	48	48 Total 36 MFNS 12 (50 µg) 12 (100 µg) 12 (200 µg) 12 Placebo
P01225	I	Safety: HPA axis	42 days	2 to 5	Allergic rhinitis	56	44 Total 22 MFNS (100 µg) 22 Placebo
C95-161	II	Dose ranging	4 weeks	6 to 11[a]	Seasonal allergic rhinitis	679	1 Total (beclometha-sone 168 µg)
I96-090	III	Efficacy/ Safety	4 weeks DB efficacy/safety; 6 months OL safety	3 to 11	Perennial rhinitis	381	91 Total 45 MFNS (100 µg) DB/ MFNS (100 µg) OL 46 Placebo DB/ MFNS (100 µg) OL
C96-094	III	Safety: Growth	1 year	3 to 9	Perennial rhinitis	98	29 Total 13 MFNS (100 µg) 16 Placebo

DB = double blind; HPA = hypothalamic-pituitary-adrenal; MFNS = mometasone furoate nasal spray; OL = open label.
a: Study C95-161 was planned for children ages 6 to 11 years only, however, one 5-year-old was enrolled into the study. Therefore, this study is included in this table for a complete review of 3- to 5-year-olds in the pediatric program.

The results of Study I96-090 demonstrated the efficacy of mometasone furoate administered once-daily in the treatment of paediatric subjects 3 to 11 years of age with perennial rhinitis based on the primary efficacy parameter, change from baseline in physician-evaluated symptom score. The overall response in terms of improvement from baseline was shown to be similar between the 3- to 5-year-old and 6- to 11-year-old subgroups. Thus there is support for efficacy in the age group 3-5 years, and no difference in efficacy is to be expected in a 3 year old as compared to a 6 year old from a pharmacological perspective. Furthermore the safety in children 3-6 years is sufficiently supported by post-marketing data from countries/regions where the product is approved.

Therefore the use of mometasone furoate in perennial rhinitis in children over 3 years of age was considered to be acceptable by the CHMP as proposed by the MAH.

Prophylaxis of seasonal allergic rhinitis

Two randomised multicentre clinical studies from the MRP dossier have been referred to, where mometasone furoate was administered to patients with a history of seasonal allergic rhinitis. Although efficacy was confirmed versus placebo in a double blinded manner, no conclusions could be drawn on whether prophylactic treatment would give fewer days of symptoms overall during a season compared to standard treatment at onset of symptoms or whether a shorter period of early treatment (< 4 weeks) would be equally effective, as there are no data available specifically addressing the appropriateness of any certain time period of relevance.

The submitted studies are not considered to support the prophylaxis of seasonal allergic rhinitis, since the data submitted for this indication are not conclusive with regard to the appropriate time point for start of treatment, considering that early start of treatment was not compared to starting at the time

of symptom onset. The onset of action of mometasone furoate in patients with allergic symptoms is rapid, and hence the observed effect after prophylactic treatment (as defined in the studies) could be related to a treatment effect as covered by the general rhinitis indication. Therefore the indication for the prophylaxis of seasonal allergic rhinitis was not accepted by the CHMP. Instead, text was introduced in Section 4.2 of the SmPC to clarify that treatment may need to be initiated a few days before the expected onset of the allergy season in patients with a history of moderate to severe symptoms of seasonal allergic rhinitis.

Nasal polyposis

The indication for the treatment of nasal polyps proposed by the MAH is approved in 26 out of 29 Member States.

Two 4-month randomized, placebo-controlled, double-blind, parallel-group multicentre, efficacy and safety treatment trials and a no-treatment, observational, follow-up study have been discussed in support of the indication for the treatment of nasal polyposis, where two doses of mometasone furoate compared with placebo (200 µg QD and BID) were investigated in a total of 664 subjects, of which 441 were treated with mometasone furoate. The indication for the treatment of nasal polyposis was accepted by the CHMP.

Although post-surgical treatment of nasal polyps was not investigated in the studies mentioned above, a study specifically investigating mometasone furoate 200 µg in preventing nasal polyp relapse after functional endoscopic sinus surgery (FESS) was performed in Sweden by the MAH, and is approved only in Sweden. The MAH has chosen not to include this indication in the proposed harmonized SmPC.

Treatment of acute sinusitis

Treatment of acute sinusitis is approved in 6 out of the 29 Member States with different wordings and restrictions. However the CHMP concluded that the submitted data was not shown to adequately target nor measure the patient population who have acute non-viral rhinosinusitis as described by the European position paper on rhinosinusitis and nasal polyps (EPOS 2007), since the primary parameter was not shown to be valid. Furthermore, the two studies investigating sinusitis submitted in support, and also the results and analysis of an additional study (A2-3852) conducted to assess the clinical relevance of the observed effect size of the treatment showed that the clinical relevance of the data generated in these studies with respect to the indication proposed had not been established.

Section 4.2 - Posology and method of administration

On the basis of 19 Phase II and III studies completed using mometasone furoate in adolescents and adults, a total dose 200 µg once daily was chosen as the standard clinical adolescent/adult dosage, allowing dose titration up to a maximum daily total dose of 400 mg.

The initial dose for rhinitis and nasal polyps is 100 µg once daily in each nostril (total daily dose of 200 µg). In case of inadequate response a dose increase to 100 µg twice daily in each nostril (total daily dose of 400 µg) has been proposed as in most Member States.

In addition, and as mentioned above, text was introduced in this section to clarify that treatment may need to be initiated a few days before the expected onset of the allergy season in patients with a history of moderate to severe symptoms of seasonal allergic rhinitis.

Paediatric population

The safety and efficacy of Nasonex Nasal Spray has not been established in:

- children under 3 years of age in seasonal allergic rhinitis and perennial allergic rhinitis
- children and adolescents under 18 years of age in nasal polyposis.

The text in section 4.2 has been revised and aligned with the quality review of documents (QRD) requirements.

Section 4.3 – Contraindications

Known hypersensitivity to the active substance, mometasone furoate, or to any of the excipients has been proposed as per the current Guideline on the summary of product characteristics.

Mometasone furoate is contraindicated in the presence of untreated localised infection involving the nasal mucosa. Herpes simplex was added as an example to the present contraindication in patients with presence of untreated localised infection involving the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, mometasone furoate has been contraindicated in patients who have experienced recent nasal surgery or trauma until healing has occurred.

Section 4.4 - Special warnings and precautions for use

The content of this section has not been changed from what is approved in most countries although the wording has in some cases been amended to achieve harmonisation.

Warnings on the immunosuppressive effects of corticosteroids are mentioned, notably on the risk of exposure of patients to certain infections (e.g., chickenpox, measles), and on the importance of obtaining medical advice if such exposure occurs.

Mometasone furoate is not recommended for use in case of nasal septum perforation, and information on the reported instances of nasal septum perforation is mentioned in section 4.8. The higher incidence of epistaxis observed in clinical studies is also mentioned in this section as well as in section 4.8. In addition, a warning concerning the presence of benzalkonium chloride excipient, which may cause nasal irritation is given. A section on the systemic effects of corticosteroids as well as reports of increased intraocular pressure following the use of intranasal corticosteroids is also mentioned. The need for concomitant use of appropriate additional therapy for additional relief of non-nasal symptoms, particularly ocular symptoms, is also highlighted.

It is also recommended that the effect on growth in the paediatric population is regularly monitored with prolonged treatment with nasal corticosteroids.

Section 4.5- Interaction with other medicinal products and other forms of interaction

Reference is made to a clinical interaction study conducted with loratadine where no interactions were reported to have been observed.

A cross reference to section 4.4 for use with systemic corticosteroids has also been included.

Section 4.6 – Fertility, pregnancy and lactation

The wording proposed by the MAH under the subheadings ‘Pregnancy’ and ‘Lactation’ was considered to be acceptable by the CHMP.

The section on ‘Fertility’ was amended to include only the relevant conclusions from non-clinical toxicity studies in accordance with current Guideline on the summary of product characteristics.

Section 4.7 - Effects on ability to drive and use machines

The statement that there are no known effects on the ability to drive and use machines was considered to be acceptable by the CHMP. This statement was already approved in most of the EU countries.

Section 4.8 - Undesirable effects

Treatment related adverse reactions such as epistaxis, pharyngitis, upper respiratory tract infection, nasal burning, nasal irritation, nasal ulceration, headache and throat irritation commonly reported in clinical studies are listed. Epistaxis, is also a very commonly reported treatment-related adverse reaction reported in ≥ 1% of patients where dosing is twice daily.

Cases of disturbances of taste and smell, nasal septum perforation, bronchospasm, dyspnoea, glaucoma, increased intraocular pressure and/or cataracts have been reported to be of unknown frequency. Cases of anaphylaxis and angioedema have also been reported (frequency unknown).

Section 4.8 was restructured as suggested by the CHMP to increase readability and to comply with the QRD template and SmPC guideline. The adverse events were presented independently of the indication and all data (pooled) were presented in a single tabulated format.

Section 4.9 – Overdose

The CHMP agreed with the MAH's proposed wording for this section, which states that inhalation or oral administration of excessive doses of corticosteroids may lead to suppression of HPA axis function and that overdose is unlikely to require any therapy other than observation since the systemic bioavailability of mometasone furoate is <1%.

Section 5.1 - Pharmacodynamic properties

This section of the proposed SmPC contains information on the mechanism of action of mometasone furoate, and its pharmacodynamic effects in patients with seasonal allergic rhinitis. The wording proposed by the MAH has already been agreed in most of the EU countries.

Data related to indications that were not retained in this harmonised SmPC were proposed for deletion and this was agreed by the CHMP.

The European Medicines Agency has waived the obligation to submit the results of studies with Nasonex Nasal Spray and associated names in all subsets of the paediatric population in seasonal and perennial allergic rhinitis (see section 4.2 for information on paediatric use). Information on this waiver was added in this section in line with the QRD requirements.

Section 5.2 - Pharmacokinetic properties

The MAH proposed a harmonised wording based on the most commonly approved label across the EU community but taking into account the QRD requirements, adding the headings absorption, distribution, biotransformation and elimination. The wording was generally agreed by the CHMP but requested amendment of the wording on distribution which is now as follows:

'Not applicable as mometasone is poorly absorbed via the nasal route.'

Section 5.3 - Preclinical safety data

The glucocorticoid-related effects of mometasone furoate observed in animal studies are described in this section.

Mometasone furoate is devoid of androgenic, antiandrogenic, estrogenic or antiestrogenic activity. No toxicological effects unique to mometasone furoate exposure were demonstrated.

Package Leaflet (PL)

The changes to the SmPC, when relevant for the user, have also been reflected in the PL and agreed by the CHMP.

The results obtained for the user testing in variation UK/H/0196/001/II/032 submitted as a commitment to a renewal in the (MRP) and approved in January 2009, were considered acceptable by the CHMP.

Nasonex is a nasal preparation for topical use and contains benzalkonium chloride. As the amount of benzalkonium chloride - 0.02 mg per actuation is above the threshold of 10 micrograms /delivered dose, a statement that Nasonex contains benzalkonium chloride, which may cause nasal irritation is included in the PL, in accordance with the Guideline on Excipients in the label and PL (2003).

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

Following the assessment of the MAH's submissions in response to the list of questions and outstanding issues raised, the CHMP accepted the following harmonised indication for Nasonex:

– treatment of the symptoms of seasonal allergic or perennial rhinitis in adults and children 3 years of age and older

- treatment of nasal polyps in adults 18 years of age and older

The indication for the prophylaxis of seasonal allergic rhinitis was not accepted by the CHMP, since the data submitted for this indication was not considered to be conclusive with regard to the appropriate time point for start of treatment, considering that early start of treatment was not compared to starting at the time of symptom onset.

The indication for the treatment of symptoms associated with acute rhinosinusitis was not accepted by the CHMP, as the data package was considered to be inconclusive and a confirmatory study was lacking.

The remaining (non)-clinical sections of the SmPC were also harmonised.

In conclusion, the revised and harmonised Product Information for Nasonex (mometasone furoate) was considered acceptable by the CHMP.

2.5. Conclusions

In conclusion, based on the assessment of the proposals submitted by the MAH and the discussions of the Committee, the CHMP adopted the harmonised product information consisting of the summary of product characteristics (SmPC), labelling and package leaflets, for Nasonex and associated names.

Based on the above, the CHMP considers the benefit-risk ratio of Nasonex and associated names to be favourable and the harmonised Product Information documents to be approvable.

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the identified divergences for the Nasonex and associated names with respect to the sections therapeutic indications, posology and method of administration, as well as the remaining sections of the SmPC;
- The committee reviewed the data submitted by the MAH from the existing clinical and non-clinical studies and post-marketing experience with Nasonex and associated names as reported by the MAH justifying the proposed harmonisation of the product information;
- The committee agreed with the harmonised summary of product characteristic, labelling and package leaflet proposed and discussed by the marketing authorisation holder;

the CHMP has recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Nasonex and associated names.