Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation

Scientific conclusions

Overall summary of the scientific evaluation of Nasonex and associated names (see Annex I)

The active ingredient of Nasonex, mometasone furoate monohydrate is a synthetic, 17-heterocyclic corticosteroid with anti-inflammatory activity. Nasonex Nasal Spray 50 mcg 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 glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, citric acid, benzalkonium chloride, and polysorbate 80.

Nasonex medicinal products are registered in the following EU Members States: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom and also in Iceland and Norway.

Nasonex medicinal products are currently not registered in Cyprus.

It was authorised according to the national procedure in 16 European countries and according to the mutual recognition procedure (MRP) in 13 Member States, with the United Kingdom (UK) acting as reference Member State (RMS).

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.

Summary of product characteristics (SmPC)

The MAH has proposed the current MRP PI that is supported by the available efficacy and safety data, as the basis for the harmonized PI.

Section 4.1 – Therapeutic Indications

Treatment of symptoms of 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 6 studies, 4 were pooled, and the patient diary results showed a reduction from baseline of 33% compared to 15% in placebo-treated patients in the first 2 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

Based on the 9 studies in the original perennial rhinitis program, the perennial rhinitis indication was approved for MRP countries in 1997, and by the other concerned Member States between 1997 and 1998. Subsequently, a study Q97-921 specifically in subjects with perennial non-allergic rhinitis (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

Information on the paediatric program and the study results (efficacy and safety) has been provided by the MAH. 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. 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. 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

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.

The MAH has chosen not to include the indication for the prevention of nasal polyp relapse after functional endoscopic sinus surgery (FESS) in the proposed harmonized SmPC, which is approved only in Sweden.

Treatment of acute sinusitis

Two studies investigating sinusitis 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. Therefore the indication for the treatment acute sinusitis was not accepted by the CHMP.

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 patients who have a history of moderate to severe symptoms of seasonal allergic rhinitis, it is recommended that mometasone furoate may need to be initiated some days before the expected start of the pollen season.

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 have not been established in nasal polyposis.

The text in section 4.2 has been revised and aligned with the 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 such as herpes simplex, involving the nasal mucosa, and also in patients who have experienced recent nasal surgery or trauma until healing has occurred because of the inhibitory effect of corticosteroids on wound healing.

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 wordings have in some cases been amended to achieve harmonisation.

Mention is made of the immunosuppressive effects of corticosteroids and the risk of exposure of patients to certain infections (e.g., chickenpox, measles), and of the importance of obtaining medical advice if such exposure occurs.

Mometasone furoate is not recommended for use in case of nasal septum perforation (the reported instances of nasal septum perforation information is mentioned in section 4.8). The higher incidence of epitaxis observed in clinical studies is also mentioned in this section as well as in section 4.8. In addition, this section gives warning concerning the presence of benzalkonium chloride excipient, which may cause nasal irritation.

A section on the systemic effects of corticosteroids including as well as reports of increased intraocular pressure following the use of intranasal corticosteroids has also been 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 was conducted with loratadine where no interactions were reported to have been observed.

A cross reference to section 4.4 for use with systemic corticosteroids is made.

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.

Section 4.8 - Undesirable effects

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 presenting all data (pooled) in a single tabulated format.

Section 4.9 – Overdose

It is stated that overdose is unlikely to require any therapy other than observation since the systemic bioavailability of mometasone furoate is <1%. However inhalation or oral administration of excessive doses of corticosteroids may lead to suppression of HPA axis function.

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 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).

Section 5.2 - Pharmacokinetic properties

The information proposed by the MAH in this section of the SmPC was listed under the headings absorption, distribution, biotransformation and elimination, and was considered to be acceptable by the CHMP, with the recommended amendments.

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).

Grounds for the variation to the terms of the marketing authorisation(s)

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 (see Annex I).