NOVARTIS

Otrivin Comp 0,5 mg/ml + 0,6 mg/ml nenäsumute, liuos

08-07-2014, Version 2.2

Public Summary of Risk Management Plan

VI.2. Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

The common cold is one of the most prevalent diseases in humans and is the most common condition for which family doctors are consulted. In the U.S. for example, an estimated one billion common colds occur per year in a population of 250 million, prompting about 25 million patients to visit their doctor for treatment. This condition affects people of all ages, with adults experiencing two to five episodes per year and children seven to ten episodes per year. Epidemiologic data suggest a peak incidence of rhinoviral colds in early autumn and late spring. Despite the usually benign nature of the illness, the common cold is a major and recurrent cause of morbidity, accounting for 40% of all time away from work and 30% of all time out of school.

The common cold is an acute viral infection of the upper respiratory tract. The symptoms of a cold are easily self-diagnosed and typically last for seven to ten days. The symptoms that generally occur first, and which are the most common, are nasal congestion, rhinorrhea and sneezing. Other common symptoms include sore throat, sinus pain, watery eyes, cough, headache, chills, muscle aches and pains.

VI.2.2 Summary of treatment benefits

Otricomb® could be used first-line in the symptomatic relief of nasal congestion and runny nose due to common cold. The combination provides relief of nasal congestion and runny nose by a topical, local action and avoids unnecessary systemic drug exposure.

VI.2.2.1 Current (gold) standards of treatment

According to the World Health Organization there is no cure treatment for cold. Therefore, the mainstay is the symptomatic treatment of cold symptoms with decongestants, cough suppressants, drugs that help remove sputum and soothing remedies.

VI.2.2.2 Where the medicinal product fits in the therapeutic armamentarium (i.e. 1st line, relapse, etc.)

Otricomb® is indicated for patients 18 years of age and older as first line option in treatment of nasal congestion and runny nose associated with common cold.

VI.2.2.3 A brief statement of the standard against which the medicine was judged: number of patients in pivotal studies and treatment regimes

The main clinical efficacy study for Otricomb® is study XY-003-IN. This study was a phase III, placebo- and active-controlled multi-centre confirmatory efficacy and safety study where a total of 786 patients were randomized to treatment with the combination product ipratropium 0.6 mg/ml with xylometazoline 0.5 mg/ml or ipratropium 0.6 mg/ml with xylometazoline 1.0 mg/ml, ipratropium 0.6 mg/ml alone, xylometazoline 1.0 mg/ml alone or placebo. Test treatment was to be taken three times daily for 24 hours and thereafter until the resolution of runny nose and nasal congestion but no longer than seven days. The primary efficacy variables were subjective ratings of severity of runny nose and nasal congestion after the first 24 hour period.

VI.2.2.4 Results in lay language

Based on the results of the main clinical efficacy study, both combinations of ipratropium and xylometazoline were superior to xylometazoline alone with respect to runny nose and superior to ipratropium alone with respect to nasal congestion. In addition, both combinations were equivalent to ipratropium with respect to runny nose and equivalent to xylometazoline with respect to nasal congestion.

VI.2.2.5 Post-authorization data which impacts on efficacy

No post-authorization efficacy data has been generated with Otricomb®.

VI.2.3 Unknowns relating to treatment benefits

In the main clinical efficacy study, the average age was 30 years (range 18-70 years), there were slightly more females (53.4%) and most patients were white Caucasian (98.2%). There is no evidence to suggest that results would be different in subjects of other races.

VI.2.4 Summary of safety concerns

Table Error! No text of specified style in document.**-1 Important identified risks**

Risk	What is known	Preventability
Increased pressure in the eyes (Intraocular pressure increased)	Based on textbook references, this has been reported in patients with angle-closure glaucoma who were receiving ipratropium nebulized solution. Increased pressure in the eyes apparently occurred when the drug solution escaped from the face mask used for nebulization and entered the eyes. Until now, approximately 10.5 million patients used Otricomb® worldwide. In the analysis of post-marketing safety data, there were 4 cases of abnormal sensation in the eye, including 3 reports of feeling of pressure in the eyes. None of these reports were medically confirmed.	Yes, by not spraying in or around the eyes.
Irregular heartbeat (Atrial	Based on a textbook reference,	Yes, by using with caution in

Risk	What is known	Preventability
fibrillation)	naphazoline (drug similar to xylometazoline) when used in the eye, may occasionally cause cardiac irregularities. Until now, approximately 10.5 million patients used Otricomb® worldwide. In the analysis of post-marketing safety data, there was one report of atrial fibrillation, however, this patient had also other health conditions that might have caused it.	patients with heart disease, raised blood pressure, overactive thyroid or diabetes.
Closure of vocal cords (Laryngospasm)	According to standard textbook reference, allergic reactions, including sudden closing of vocal cords which obstructs breathing (laryngospasm), have been reported in patients receiving ipratropium inhalation through their mouth. These were aerosol formulations used in the mouth and not sprays used in the nose such as Otricomb®. Until now, approximately 10.5 million patients used Otricomb® worldwide. In the analysis of post-marketing safety data, there were no reports of laryngospasm.	Yes, by avoiding use in patients with allergy to ipratropium, atropine and other similar drugs or xylometazoline.
Throat swelling (Pharyngeal oedema)	According to standard textbook reference, allergic reactions, including throat swelling, have been reported in patients receiving ipratropium inhalation through their mouth. These were aerosol formulations used in the mouth and not sprays used in the nose such as Otricomb®. Until now, approximately 10.5 million patients used Otricomb® worldwide. In the analysis of post-marketing safety data, there were four non-serious reports of throat swelling including one medically confirmed report of mild allergic reaction with short-lasting throat problems.	Yes, by avoiding use in patients with allergy to ipratropium, atropine and other similar drugs or xylometazoline

Table Error! No text of specified style in document.**-2 Important potential risks**

Risk	What is known
Altered or lost taste and smell	The use of Otricomb® may temporally alter taste and smell. Although a few reports of complete taste and smell loss have been received from consumers, there is no conclusive

Risk	What is known
	evidence that Otricomb® caused these events. Importantly, taste and smell loss are often a consequence of the upper respiratory tract disorders that affect Otricomb® users. Patients should seek medical advice as soon as these events are noted.
Rebound nasal congestion (Rhinitis medicamentosa) in longer term use	Prolonged use of nasal decongestants may induce rebound nasal congestion without mucus discharge or sneezing. No such cases he been reported with Otricomb®. However, it is important to limit treatment to a maximum of seven days to prevent any possible rebound effect.
Overdose	Following the nasal application of Otricomb®, the blood levels of xylometazoline and ipratropium are very low. Accordingly, post-marketing experience has not indicated any particular safety concern in patients that sprayed excessive amounts of the product. However, there is a remote possibility that excessive administration of xylometazoline causes severe dizziness, perspiration, severely lowered body temperature, headache, reduced heart rate, high blood pressure followed by low blood pressure, respiratory depression, coma and convulsion. Small children are more sensitive to toxicity than adults. Excessive ipratropium could cause an increase in heart rate, dry mouth and vision problems. Patients should immediately seek help from a physician if such symptoms develop.
Off-label use (wrong indication)	Otricomb® is indicated for the symptomatic treatment of nasal congestion and rhinorrhea (runny nose) in connection with common colds. No particular concerns regarding use for wrong indications have emerged so far from Novartis post-marketing safety database.
Use in elderly patients above 70 years of age	There is only limited experience of use in elderly patients. However, the safety profile in this population is expected to be similar to that of younger adults. No particular safety concerns have been identified to date.
Use in children and adolescents <18 years of age	Otricomb® should not be used in children and adolescents below 18 years of age due to lack of sufficient data. No particular safety concerns have been identified to date.
Use during pregnancy and lactation	Due to the lack of adequate data in pregnancy, the potential risk for humans is unknown. Therefore, Otricomb® should not be used in pregnancy unless clearly necessary. Following the nasal application of Otricomb®, the blood levels of xylometazoline and ipratropium are very low. Therefore, if the mother uses Otricomb®, any effects on the breast-fed infant are unlikely. However, since no specific studies exist, the mother's need for treatment with Otricomb® and the advantages of breast-feeding must be weighed against the potential risks to the infant.
Drug-drug interactions	Drugs that may interact with Otricomb® include: monoaminoxidase inhibitors (MAO inhibitors) used for depression, Tri- and tetracyclic antidepressants, and medications containing anticholinergic substances such as

Risk	What is known
	treatments for travel sickness and gut disorders. Concomitant use with MAO inhibitors and Tri- and tetracyclic antidepressants is not recommended. No other possible interactions are known.

Table Error! No text of specified style in document.**-3 Missing information**

Risk	What is known
None	Not applicable

VI.2.5 Summary of additional risk minimization measures by safety concern

No additional risk minimization measures are deemed necessary.

VI.2.6 Planned post authorization development plan

No post-authorisation development plan is planned.

VI.2.6.1 List of studies in post authorization development plan

Not applicable.

VI.2.6.2 Studies which are a condition of the marketing authorization

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

The first RMP (version 1.0) on xylometazoline hydrochloride / ipratropium bromide was released on 26th May 2010. The next version of the RMP (version 2.0) was submitted in June 2013 in the EU (MRP). Since the RMP (version 2.0) contained new potential safety risks (ageusia and anosmia), the RMS (Swedish Health Authority) was of the opinion that the proposed change has the potential to have a significant impact on the safety of the medicinal product. This potential impact has to be evaluated accordingly during an assessment; hence this RMP should be upgraded to a variation type II. As agreed with the RMS, an updated RMP (version 2.1) to reflect the proposed changes in the SmPC (Nov. 2013) was submitted Feb. 2014, and RMP (version 2.0) was withdrawn.

The RMP (version 2.1) provides key information on new important potential safety risks anosmia and ageusia; and new important identified safety risks including intraocular pressure increased, atrial fibrillation, laryngospasm, and pharyngeal oedema.

Additionally, the format of RMP version 2.1 is different from RMP version 1.0 in order to more fully comply with the EMA Guideline on Risk Management Systems for Medicinal Products for Human Use (EMA/838713/2011).

This newly updated RMP (version 2.2) addresses comments raised by the Swedish Health Authority at Day 59 in the request for supplementary information (RSI) dated 26 May 2014. Section 13.2 regarding Elements for a Public Summary has been updated. Paragraphs have been condensed and rewritten in lay language.