IPAR

HEALTH PRODUCTS REGULATORY AUTHORITY

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

SCIENTIFIC DISCUSSION

PA0678/120/005

OTRIVINE ADULT MUCUS RELIEF MENTHOL 0.1%W/V NASAL SPRAY

XYLOMETAZOLINE HYDROCHLORIDE

THE PUBLIC ASSESSMENT REPORT REFLECTS THE SCIENTIFIC CONCLUSION REACHED BY THE HEALTH PRODUCTS REGULATORY AUTHORITY (HPRA) AT THE END OF THE EVALUATION PROCESS AND PROVIDES A SUMMARY OF THE GROUNDS FOR APPROVAL OF A MARKETING AUTHORISATION FOR A SPECIFIC MEDICINAL PRODUCT FOR HUMAN USE. IT IS MADE AVAILABLE BY THE HPRA FOR INFORMATION TO THE PUBLIC, AFTER DELETION OF COMMERCIALLY SENSITIVE INFORMATION. THE LEGAL BASIS FOR ITS CREATION AND AVAILABILITY IS CONTAINED IN ARTICLE 21 OF DIRECTIVE 2001/83/EC, AS AMENDED. IT IS A CONCISE DOCUMENT WHICH HIGHLIGHTS THE MAIN PARTS OF THE DOCUMENTATION SUBMITTED BY THE APPLICANT AND THE SCIENTIFIC EVALUATION CARRIED OUT BY THE HPRA LEADING TO THE APPROVAL OF THE MEDICINAL PRODUCT FOR MARKETING IN IRELAND.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Otrivine Adult Mucus Relief Menthol from Novartis Consumer Health UK Limited on 4th July 2014

- the relief of nasal congestion due to colds, hay fever or other allergic rhinitis, sinusitis.

-To aid drainage of secretions in affections of the paranasal sinuses.

-As an adjuvant in otitis media, to decongest the nasopharyngeal mucosa.
-To facilitate rhinoscopy.

The legal basis of the application is Article 8(3) 'known active substance' of Directive 2001/83/EC. This application is a national line extension application based on Otrivine Adult 0.1% w/v Nasal Drops, PA 30/26/1.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at http://www.hpra.ie/

Name of the product	Otrivine Adult Mucus Relief Menthol 0.1% w/v Nasal Spray
Name(s) of the active substance(s) (INN)	XYLOMETAZOLINE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	R01AA07
Pharmaceutical form and strength (s)	0.1% w/v
Marketing Authorisation Number (s) in Ireland (PA)	PA0678/120/005
Marketing Authorisation Holder	GlaxoSmithKline Consumer Healthcare (Ireland) Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Otrivine Adult Mucus Relief Menthol 0.1% w/v Nasal Spray.

II.2 Drug substance

The active substance is Xylometazoline Hydrochloride an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The drug product is a nasal spray.

Otrivine Adult Mucus Relief Menthol 0.1% w/v nasal spray contains 1 mg/ml of xylometazoline hydrochloride. Each metered-dose spray delivers 0.14 mg of xylometazoline hydrochloride.

The other ingredients are: sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, sodium chloride, disodium edetate, levomenthol (menthol), cineole (eucalyptol), sorbitol, polyoxylhydrogenated castor oil (macrogol glycerol hydroxystearate) and purified water.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for nasal preparations and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as a HDPE bottle mounted with a metered dose spray pump.

Evidence has been provided that the packaging complies with relevant Ph.Eur. requirements and EU legislation for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 30 months when the product is not stored above 25°C.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Otrivine Adult Mucus Relief Menthol 0.1% w/v Nasal Spray.

III NON-CLINICAL ASPECTS

III.1 Introduction

This application concerns Otrivine Adult Mucus Relief Menthol 0.1%w/v Nasal Spray, which contains xylometazoline hydrochloride 1 mg/ml as active ingredient. This is a line extension based on Otrivine Adult 0.1% w/v Nasal Drops. Otrivine 0.1% nasal solutions are well-established topical nasal decongestants, and have been marketed for over 50 years and are currently approved in over 120 countries worldwide.

No new preclinical data have been submitted. The pharmacology, pharmacokinetics and toxicology of the active substance are well established. This assessment is limited to the overview of the toxicology of the novel excipients menthol and eucalyptol.

Menthol
Menthol is an excipient used as a flavouring agent or odour enhancer, approved for use in food with an acceptable daily intake (ADI) of 0.4 mg/kg body weight per day. Toxicity studies in rats and mice did not show any evidence of carcinogenicity, and mutagenicity or teratogenicity studies did not indicate any safety concerns.

Eucalyptol
Cineole (eucalyptol, 1,8 cineole), is widely distributed in plants and used as a flavouring agent in food and medicinal products. In 28-day studies in rats menthol was associated with toxicity in kidneys, liver a and brain (increased brain weight) at high doses which are not relevant to exposure resulting from use of Otrivine Menthol 0.1% nasal spray. Long term oral exposure in mice was not associated with any toxicity findings. Eucalyptol was gentotoxic in a sister chromatid exchange assay but negative in all other assays. Conventional carcinogenicity and reproducitive toxicity studies are not available.

III.2 Discussion on the non-clinical aspects

As the active substance xylometazoline hydrochloride is well established, non-clinical data have been superseded by clinical experience. Therefore new non-clinical studies are not required. Based on the available nonclinical data, the excipients menthol and eucalyptol are not considered to pose a safety concern.

IV CLINICAL ASPECTS

IV.1 Introduction

Otrivine 0.1% nasal solution (drops, spray and metered-dose spray) is a well-established topical nasal decongestant, containing xylometazoline hydrochloride at a concentration of 0.1% weight/volume. Otrivine is currently approved in over 120 countries.

Otrivine 0.1% nasal solution is available in different formulations, which have been developed with the aim to achieve best individual patients' acceptability and tolerability.
The formulations are: Otrivine 0.1% F2, Otrivine 0.1% F5, Otrivine 0.1% F3 (preservative-free),Otrivine Menthol 0.1% F4, and Otrivine Menthol 0.1% F6 (preservative-free).
This application concerns the Otrivine Menthol 0.1% F6 (preservative-free) formulation and reviews the relevant data in support of an application for a national line extension based on the already approved Otrivine formulations.
The active ingredient of Otrivine Menthol 0.1% nasal spray is xylometazoline 0.1%, which is a sympathomimetic agent acting on the alpha adrenergic receptors in the nasal mucosa.
Xylometazoline is one of the most commonly used topical nasal decongestants, providing safe and effective symptomatic relief in patients suffering from nasal congestion (Eccles 2010).

The excipients menthol and eucalyptol do not contribute to the pharmacological effect, but have well-known effects on sensory receptors, providing a fresh scent and a cooling sensation.
The formulation is preservative-free. Otrivine Menthol 0.1% nasal spray F6 is intended for over-the-counter (OTC) use in adults and adolescents over 12 years of age. The indications of Otrivine include the relief of nasal congestion due to colds, hay fever or other allergic rhinitis, and sinusitis. Otrivine is also
indicated to aid drainage of secretions in affections of the paranasal sinuses, as adjuvant in the treatment of otitis media

to decongest the nasopharyngeal mucosa, and to facilitate rhinoscopy.

IV.2 Pharmacokinetics

Plasma concentrations of xylometazoline in man after local nasal application of the product are very low and close to the limit of detection.

IV.3 Pharmacodynamics

Xylometazoline is a sympathomimetic agent acting on alpha-adrenergic receptors in the nasal mucosa. Administered in the nose, it constricts the nasal blood vessels, thereby decongesting the mucosa of the nose and neighbouring regions of the pharynx. This decongests nasal passages and enables patients suffering from blocked nose to breathe more easily through the nose. The effect of Otrivine Adult Mucus Relief Menthol, 0.1% w/v Nasal Spray begins within a few minutes and lasts for up to 10 hours.

In a double-blind, saline solution controlled study in patients with common cold, the decongestant effect of Otrivine was significantly superior ($p<0.0001$) to saline solution based on rhinomanometry measurement. Relief of blocked nose developed twice as fast in the Otrivine group compared to saline solution as of 5 minutes post treatment ($p= 0.047$).

Otrivine Adult Mucus Relief Menthol, 0.1% w/v Nasal Spray is well tolerated, even by patients with a sensitive mucosa, and does not impair the mucociliary function.

Otrivine Adult Mucus Relief Menthol, 0.1% w/v Nasal Spray contains no preservative. The one-way vacuum pump delivering the metered dose spray is specifically designed to prevent microbial contamination of the content. The nozzle has a special design and a cap with special openings that allow the residual liquid to dry, thus preventing microbial contamination of the next sprayed dose.

Otrivine Adult Mucus Relief Menthol, 0.1% w/v Nasal Spray contains cooling aromatic vapours of menthol and eucalyptol (cineole) in addition to the active ingredient xylometazoline.

IV.4 Clinical Efficacy

Otrivine (xylometazoline) is a well-known topical nasal decongestant, which is currently approved for marketing in over 120 countries. Its efficacy and safety are well established.
A large number of clinical studies have previously been performed showing efficacy of topical xylometazoline in patients suffering from nasal congestion. Since this application is for a line extension of an approved product, they are not discussed in this Overview of Efficacy.

No dose-finding study has been performed with the Otrivine Menthol 0.1% formulation. The strength of xylometazoline 0.1% is well established for use in adults as of 12 years of age.

The efficacy of Otrivine 0.1% nasal solution as a decongestant is demonstrated by both objective and subjective measures in an adequate placebo-controlled efficacy/safety study. This conclusion is corroborated by two active-controlled studies (one pharmacological studyand one tolerability/acceptability study), which confirm the objective and the subjective measures of nasal decongestion, respectively.
Upper airway conductance at one hour post-dose, which was the primary endpoint of theefficacy/safety study, was significantly improved with Otrivine 0.1% vs. placebo. Thedecongestant effect in the Otrivine group lasted for up to 12 hours. The clinical relevance of this effect was shown by significant differences of subjective VAS ratings between active and placebo (> 10 mm for peak relief of congestion), despite the well-known placebo-effect of the control saline solution. With Otrivine, relief of blocked nose developed within 5 minutes post
treatment, which was twice as fast as with placebo. The clinical importance of the effect was further supported by a significant improvement of common cold symptoms over several days.
Due to the fact that the excipients menthol and eucalyptol have no influence on nasal airway resistance/conductance, these efficacy conclusions can be bridged and can be considered valid for the Otrivine Menthol F4 and Otrivine

Menthol Preservative-free F6 formulations.

IV.5 Clinical Safety

Otrivin 0.1% nasal solution was well tolerated in the recent, adequately controlled efficacy / safety study and no safety issue was identified. Tolerability and acceptability of the excipients menthol and eucalyptol have been evaluated in an active-controlled study.
The benzalkonium-free Otrivin Menthol 0.1% nasal spray formulation contributes to the good tolerability by avoiding any adverse effect of the preservative on the nasal mucosa.
Extensive post-marketing experience with the different Otrivin nasal formulations, amounting to over 5 million patient-years between July 1st 2009 and May 31st 2011, has not identified any new relevant safety finding. In particular, there is no concern regarding an increased riskof adverse events with the Otrivin Menthol F4 and F6 formulations as compared with the nonmentholated forms of Otrivin.

The schedule for Periodic Safety Update Reports (PSUR) submission should be addressed.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

Otrivine nasal solution is indicated for the relief of nasal congestion due to colds, hay fever or other allergic rhinitis and sinusitis. It is also indicated to aid drainage of secretions in affections of the paranasal sinuses, as an adjuvant in the treatment of otitis media to decongest the nasopharyngeal mucosa, and to facilitate rhinoscopy. Otrivine Menthol 0.1% nasal spray is recommended for adults and adolescents over 12 years of age. It is recommended for the short-term use until disappearance of symptoms and patients are advised not to take decongestants for more than ten consecutive days.

Summary of Clinical Benefits

Otrivine 0.1% nasal solution provides effective relief in nasal congestion as demonstrated by both objective and subjective measures in an adequate placebo-controlled efficacy/safety study. This conclusion is corroborated by two active-controlled studies (one pharmacological study and one tolerability/acceptability study). Relief of congestion develops within the first minutes of treatment and is sustained for up to 12 hours. Otrivine Menthol 0.1% nasal spray provides patients with the choice of a fragranced, preservative-free formulation. The excipients menthol and eucalyptol, which do not alter airway resistance, add a fresh scent and a cooling sensation. The preservative-free formulation prevents any possible irritation of the nasal mucosa from benzalkonium.

Summary of Risks
Xylometazoline is a well-known and widely used nasal decongestant, which presents no relevant unanswered risk questions. Tolerability of the excipients menthol and eucalyptol has been established for Otrivine and other nasal decongestants.
Due to the topical mode of administration of Otrivine 0.1% nasal solution, systemic exposure is very low, limiting the risk of any systemic side effects and of interactions with other drugs.

V OVERALL CONCLUSIONS

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Otrivine Adult Menthol Mucus Relief from Novartis Consumer Health UK Limited on 4th July 2014

- the relief of nasal congestion due to colds, hay fever or other allergic rhinitis, sinusitis.

-To aid drainage of secretions in affections of the paranasal sinuses.

-As an adjuvant in otitis media, to decongest the nasopharyngeal mucosa.

-To facilitate rhinoscopy.

The legal basis of the application is Article 8(3) ‘known active substance’ of Directive 2001/83/EC. This application is a national line extension application based on Otrivine Adult 0.1% w/v Nasal Drops, PA 30/26/1.

Otrivine has been shown to be safe and effective in providing relief of nasal congestion in the patient population for whom the product is intended. Extensive post-marketing experience of various Otrivine formulations over the past 50 years indicates that the product is well tolerated in a broad patient population under various conditions of use.

In conclusion, the presented data confirm a favorable benefit-risk profile of Otrivine Menthol 0.1% nasal spray in the relief of nasal congestion due to colds, hay fever or other allergic rhinitis, and sinusitis, to aid drainage of secretions in affections of the paranasal sinuses, as adjuvant in the treatment of otitis media to decongest the nasopharyngeal mucosa, and to facilitate rhinoscopy.

VI REVISION DATE

July 2016

VII UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

Scope	Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/ non approval
Transfer	N/A	MAH & PA number		29th July 2016	Approved