LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Otrivin Menthol Preservative-Free Nasal Spray 0.1%
Xylometazoline hydrochloride

SE/H/628/01/MR

This module reflects the scientific discussion for the approval of Otrivin Menthol. The procedure was finalised at 19th October 2006. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

Fastställare: Anita Finne Grahnén Datum: 2006-10-13

I. INTRODUCTION

Novartis Sverige AB has applied for a marketing authorisation for Otrivin Menthol Preservative-Free Nasal Spray 0.1 %. The active substance xylometazoline hydrochloride is the same as in Otrivin Preservative Free, marketed by Novartis Sverige AB since 1996. The product is indicated for the treatment of Rhinitis. For decongestion in sinusitis and for facilitating rhinoscopy.

II. QUALITY ASPECTS

II.1 Introduction

Otrivin Methol is presented in the form of nasal spray. 1 ml contains 1.0 mg xylometazoline hydrochloride. The excipients are menthol, cineole, disodium edetate, sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, sodium chloride, sorbitol, macrogol glycerol hydroxystearate, purified water. The product is packed in a HDPE bottle with dosing pump.

II.2 Drug Substance

Xylometazoline hydrochloride has a monograph in the Ph Eur and the manufacturer holds a CoS of the monograph.

Xylometazoline is a white or almost white, crystalline powder and is freely soluble in water, in ethanol and in methanol. The structure has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Otrivin Menthol Nasal Spary is formulated using excipients described in the current Ph Eur, except for cineole which is controlled according to Ph. Helv. All raw materials used in the product are of vegetable origin or has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance. The compatibility of the container/closure with the finished product has been investigated due to the fact that multidose containers for pharmaceutical preparations without antimicrobial preservatives must satisfy special criteria. A report from the test of microbial tightness of the primary packaging for Otrivin menthol nasal solution without

preservatives has been submitted. The container and closure interaction with the product has also been studied. Both sorption of solution ingredients to the container and leaching (extraction) of plastic additives to the content have been studied. The bottle is suitable for its intended use.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 25°C.

III. NON-CLINICAL ASPECTS

Since Otrivin Menthol is a line extension to Otrivin, with the odour being the only difference, further pre-clinical data have not been submitted and is not considered necessary.

IV. CLINICAL ASPECTS

Since Otrivin Menthol is a line extension to Otrivin, with the odour being the only difference, further clinical data have not been submitted and is not considered necessary.

When Otrivin Menthol (with preservative) was originally applied for in 1995 in Sweden, the rational for adding menthol was discussed. Hypersensitivity reactions due to menthol have been reported and the pleasant smell of menthol could potentially lead to overuse. However, the already included general warning on hypersensitivity in the SPC was considered sufficient and the other issue would not be reasons for refusal. Menthol is widely used in many, not medical, products and the experience would be considered as very large. Hence, any serious safety problems must be considered highly unlikely. This is further confirmed by the post-marketing data submitted by the MAH.

Since menthol has been regarded simply as a flavouring agent, the PSUR:s have not been separated between Otrivin with and without menthol. In 2003 in association with renewal, the MPA raised some questions around potential CNS-related adverse events due to menthol. A case with a 13-year-old boy with CNS-symptoms after inhaling a mixture containing menthol (4.1%) among other excipients (eucalyptus and peppermint oils) had been reported. In response to this, the MAH clarified that there were no CNS events reported for Otrivin during the period (2001-01-01 – 2003-10-20) and that the amount of menthol in Otrivin Menthol, 0.03%, is 1000 times lower than the concentration generally considered to induce CNS effects.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed. The justification for absence of user testing is acceptable.

The risk/benefit ratio is considered positive and Otrivin Methol Preservative-Free 0.1 % Nasal Spary is recommended for approval.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

Fastställare: Anita Finne Grahnén Datum: 2006-10-13