LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bufomix Easyhaler
(budesonide, formoterol fumarate dihydrate)

SE/H/1213/04/DC

This module reflects the scientific discussion for the approval of Bufomix Easyhaler. The procedure was finalised on 2016-02-11. 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

I. INTRODUCTION

Orion Corporation has applied for a marketing authorisation for Bufomix Easyhaler, inhalation powder, 80 micrograms/4.5 micrograms/inhalation. The active substances budesonide and formoterol fumarate dihydrate are the same as in Bufomix Easyhaler, inhalation powder, 160 micrograms/4.5 micrograms and 320 micrograms/9 micrograms per inhalation, marketed by Orion Corporation since 2014.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

Bufomix Easyhaler is not considered to pose any risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

No studies have been conducted with the 80 µg/4.5 µg strength. In the previous application for the higher strengths, therapeutic equivalence was concluded based on four pharmacokinetic studies with the 320 µg/9 µg strength. Extrapolation of data from the highest strength to the 80 µg/4.5 µg strength is considered acceptable since dose proportionality in vitro has been shown for both budesonide and formoterol fumarate.

IV.2 Efficacy and safety

No studies have been conducted with the 80 µg/4.5 µg strength which is acceptable. The only new clinical aspect to consider for the 80 µg/4.5 µg strength is the age limit for treatment i.e. 6 years whereas the higher strength has an age limit of 12 years. The applicant has justified the absence of specific clinical data in children 6-12 years by the following:

1) The flow rate dependency *in vitro* for the different devices is considered similar.

2) The peak inspiratory force *in vivo* for the different devices is considered similar.

3) There is extensive experience of the use of Easyhaler in children.

4) The PK-profile in children and adults is similar.

5) The corresponding mono-component products (Giona Easyhaler and Formoterol Easyhaler are approved in EU from 6 years of age.

IV.3 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bufomix Easyhaler.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns associated with Bufomix Easyhaler maintenance therapy	
Important identified risks	Systemic GCS effects Cardiac LABA effects Life-threatening and fatal asthma events Pneumonia in COPD Hypersensitivity reactions including anaphylactic reactions Bronchospasm
Important potential risks	-
Missing information	Use in patients with hepatic impairment Use in patients with renal impairment Use during pregnancy Use during breastfeeding Effect on fertility

Summary of additional safety concerns associated with Bufomix Easyhaler maintenance and reliever therapy	
Important identified risks	-
Important potential risks	Off-label use
Missing information	-

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Bufomix Easyhaler, 160 micrograms/4.5 micrograms/inhalation, Inhalation Powder, SE/H/1213/02/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application concerns Bufomix Easyhaler, inhalation powder, 80 micrograms/4.5 micrograms/inhalation. This is a lower strength to the approved strengths

160 micrograms/4.5 micrograms/inhalation and 320 microgram/9 micrograms/inhalation (SE/H/1213/02-03/DC). This lowest strenght was also part of the initial application, but withdrawn at day 197 of the procedure due to outstanding concerns from one MS.

Dose proportionality *in vitro* has been shown for both budesonide and formoterol fumarate and it is considered acceptable to waive *in vivo* studies for this strength.

This strength is intended for children from 6 years of age. In the previous application the applicant provided a justification for the lack of specific clinical studies conducted in children. This justification is accepted by the RMS.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Bufomix Easyhaler, inhalation powder, 80 micrograms/4.5 micrograms/inhalation was positively finalised on 2016-02-11.

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