LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fluticasone Cipla
(Fluticasone propionate)

SE/H/1284/01-02/DC

This module reflects the scientific discussion for the approval of Fluticasone Cipla. The procedure was finalised at 2013-06-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Cipla (EU) Limited has applied for a marketing authorisation for Fluticasone Cipla, pressurised inhalation, suspension, 125 and 250 micrograms/actuation claiming essential similarity to Flixotide standard 125 Mikrogramm and Flixotide forte 250 Mikrogramm - Dosieraerosol authorised in AT since 1994, with GlaxoSmithKline Pharma GmbH, Wien as marketing authorisation holder. The product contains fluticasone propionate as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is FLIXOTIDE 250 microgrammes/dose, suspension for inhalation in pressurised bottle from UK with Laboratoire GLAXOSMITHKLINE, France as marketing authorisation holder.

II. QUALITY ASPECTS

II.1 Introduction

Fluticasone Cipla is presented in the form of pressurised inhalation, suspension containing 125 microgram or 250 microgram per actuation of fluticasone propionate. The only excipient is norflurane (HFA 134a). The suspension is filled in an aluminium canister fitted with a suitable metering valve and a plastic actuator.

II.2 Drug Substance

Fluticasone propionate has a monograph in the Ph Eur.

The drug substance is a white or almost white powder which is practically insoluble in water and slightly soluble in alcohol. The structure of fluticasone propionate 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 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

Fluticasone Cipla pressurised inhalation, suspension is formulated using a excipient which is controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as particle size.

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 not stored in refrigerator or freezer.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the 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.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The pharmacokinetic documentation consists of two studies to evaluate bioequivalence after inhalation of fluticasone with and without the aid of a Volumatic spacer.

Bioequivalence was observed between the 250µg test formulation and the 250µg reference formulation of Flixotide when administered in a single dose study to healthy volunteers both with and without a spacer.

Study 11-08-041 was a single-dose, four-way crossover study conducted in 32 healthy volunteers with the 250 µg strength (administered as 4 puffs, i.e. a total dose of 1000 µg). The test and reference products were administered without a spacer.

Study PRC/CRD/02/12 was a single-dose, two-way crossover study conducted in 28 healthy volunteers with the 250 µg strength (administered as 4 puffs, i.e. a total dose of 1000 µg). The test and reference products were administered with a Volumatic spacer.

Both studies were conducted without active charcoal blockade. The gastro-intestinal absorption of fluticasone is less than 1% and considered as negligible. Hence, a study without charcoal blockade is sufficient as it will not only reflect pulmonary deposition but also total systemic exposure of fluticasone. Since Fluticasone Cipla is a pressurised metered dose inhaler, there is no flow-dependency of the product. Evaluation of bioequivalence in healthy volunteers is considered acceptable. Plasma concentrations of fluticasone were evaluated using an LC/MS/MS-method. In both studies bioequivalence was demonstrated for fluticasone AUC and $C_{max.}$ The T_{max}-values were similar for the test and reference product.

Dose proportionality has been shown for the two applied strengths.

To summarize: therapeutic equivalence has been sufficiently demonstrated by pharmacokinetic

data.

IV.2 Discussion on the 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 clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

A handling study was not required, as the product is administered as a pMDI, and the handling of the test and reference product are very similar.

Whereas the reference product is approved in three strengths (50, 125 and 250 micrograms/actuation), this application concerned only the two higher strengths (125 and 250 mcg). Therefore, this product does not have an indication in children and adolescents 4-15 years of age.

To ensure that patients are not receiving a higher maintenance dose than required, a statement has been introduced in section 4.2 of the SmPC, advising the prescriber to swap to a different fluticasone propionate inhalation product in case a lower maintenance dose is needed.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive in adults and adolescents aged 16 years and above, and Fluticasone Cipla, pressurised inhalation, suspension, 125 and 250 micrograms/actuation is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Fluticasone Cipla, pressurised inhalation, suspension, 125 and 250 micrograms/actuation was successfully finalised on 2013-06-11.

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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)

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