LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Truflo
(fluticasone propionate)

SE/H/1367/01-02/DC

This module reflects the scientific discussion for the approval of Truflo. The procedure was finalised on 2014-09-25. 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

The application for Truflo,125 and 250 micrograms/actuation, pressurised inhalation, suspension, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Cipla Europe NV, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, ES, FI, HU, IT and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Flixotide standard 125Mikrogramm and Flixotide forte 250 Mikrogramm - Dosieraerosol, authorised in AT since 1994, with GlaxoSmithKline Pharma GmbH, Wien as marketing authorisation holder.

The reference product used in the bioequivalence study is Flixotide 250 microgram Evohaler, suspension for inhalation in pressurised bottle from UK with GLAXOSMITHKLINE as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Truflo 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

Truflo 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

According to the OIP-guideline (CPMP/EWP/4151/00 rev 1) a step-wise approach should be considered when demonstrating therapeutic equivalence. The first step consists of pharmaceutical data, the second step of pharmacokinetic data and the third step is represented by pharmacodynamic/clinical efficacy and safety data.

In the current application, the data do not comply with all pharmaceutical criteria of the guideline. Therefore, the application cannot be based solely on *in vitro* data and *in vivo* studies are needed for demonstration of therapeutic equivalence. The Applicant did therefore continue with Step 2, pharmacokinetic studies, to demonstrate therapeutic equivalence.

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.

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 Truflo is a pressurised metered dose inhaler, there is no flow-dependency of the product. Evaluation of bioequivalence in healthy volunteers is therefore acceptable. Plasma concentrations of fluticasone were evaluated using an adequately validated 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. The highest strength (250

microgram/actuation) deviates slightly more in fine particle mass and might be considered as worst case strength. Hence, the results of the bioequivalence studies with the highest strength could be extrapolated to the lower strength.

Equivalence with the reference product has been satisfactorily demonstrated.

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.

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 and Truflo,125 and 250 micrograms/actuation, pressurised inhalation, suspension is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Truflo,125 and 250 micrograms/actuation, pressurised inhalation, suspension was successfully finalised on 2014-09-25.

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