LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Arquist
(fluticasone propionate)

SE/H/1580/01-02/DC

This module reflects the scientific discussion for the approval of Arquist. The procedure was finalised on 2016-12-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Arquist, pressurised inhalation, suspension, 125 and 250 micrograms/actuation is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Cipla (EU) Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, FR, IS and LU 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 mcg Evohaler, suspension for inhalation in pressurised bottle from UK with GLAXOSMITHKLINE as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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

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 evaluating 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 the application concerns 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 Cmax. The Tmax-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.

The pharmacokinetic documentation is sufficient.

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.

IV.3 Risk Management Plan

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 Arquist.

The MAH has submitted RMP (Version 2), dated 21 January 2016. The Summary of Safety Concerns is presented below:

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions, including anaphylactic reactions • Systemic effect of corticosteroids • Hyperglycaemia • Psychiatric disorders • Ocular events (cataract, glaucoma)
Important potential risk	• Paradoxical bronchospasm • Adrenal suppression • Off label use in children below 16 years of age • Off label use in COPD
Missing information	• Pregnancy and breastfeeding women. • Patients with hepatic impairment • Effect of fluticasone on fertility
Important identified interactions	• Interaction with cytochrome P4503A4 • Interaction with CYP3A inhibitors

The Applicant proposes routine pharmacovigilance and routine risk minimisation activities for monitoring the safety of this product, which is endorsed.

The RMP is approvable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application concerns Arquist, pressurised inhalation, suspension formulated in two different strengths; i.e. 125 microgram/actuation and 250 microgram/actuation. The product is applied as a hybrid application and evaluated in a step-wise approach according to the guideline CPMP/EWP/4151/00 Rev.1.

The base in the evaluation is the pharmaceutical properties. Comparative *in vitro* studies of the applied product and the reference product have been performed on both strengths and statistical analysis is provided for grouped stages of the aerodynamic particle size distribution. 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.

To support this application with respect to clinical aspects, the Applicant has submitted a review of published clinical data and two pharmacokinetic studies conducted in healthy volunteers, with the 250 μg formulation. Bioequivalence was evaluated both with and without administration with the aid of a spacer. The review of published data is considered adequate. The design of the bioequivalence studies is adequate to evaluate pulmonary deposition (efficacy) and total systemic exposure (safety). The batches, test and reference, used in the PK studies both with and without spacer have been shown to be representative for the product

applied for and for the reference product on the market. The absence of studies with the additional lower strength (125 μg) is acceptable, since it has been shown that that the highest strength (250 μg) deviates most in fine particle mass and might be considered as worst case. Further, dose proportionality has been shown for the two strengths. Bioequivalence has thus been satisfactorily demonstrated.

The indication treatment of bronchial asthma in adults and adolescents aged 12 years and above is considered approvable from a clinical point of view as for the reference product, the posology in adolescents is the same as that in adults and no relevant differences between a 12 year old adolescent and an adult are expected. To ensure that patients are not receiving a higher maintenance dose than required, a statement has been introduced in section 4.2 advising the prescriber to swap to a different fluticasone propionate inhalation product in case a lower maintenance dose is needed. This is endorsed. The posology is in line with that approved for the reference product, i.e. 50-500 mcg twice daily.

To conclude, the application contains an adequate review of published clinical data and bioequivalence for the 125μg and 250 μg strengths has been shown. The indication treatment of bronchial asthma in adults and adolescents aged 12 years and above is considered approvable.

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 Mutual recognition/Decentralised procedure for Arquist, Pressurised inhalation, suspension, 125 micrograms per actuation, 250 micrograms per actuation, was positively finalised on 2016-12-08.

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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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