CBG MEB

Public Assessment Report

Scientific discussion

Fluticasonpropionaat Xiromed 0.5 mg/g cream

(fluticasone propionate)

NL/H/3524/001/DC

Date: 6 June 2019

This module reflects the scientific discussion for the approval of Fluticasonpropionaat Xiromed 0.5 mg/g cream. The procedure was finalised on 14 December 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fluticasonpropionaat Xiromed 0.5 mg/g cream, from Exeltis Healthcare S.L.

For adults and children aged 3 months and over
The product is indicated in adults for symptomatic treatment of inflammatory dermatoses not caused by micro-organisms and responsive to corticosteroids such as:

- Psoriasis (excluding widespread plaque psoriasis)
- Lichen planus
- Lichen sclerosus and atrophicus
- Lichenifications
- Discoid lupus erythematosus
- Pustulosis palmaris and plantaris
- Mycosis fungoides
- Granuloma annulare

For children
For children aged 3 months and over who are unresponsive to lower potency corticosteroids, the product is indicated for the relief of the inflammatory and pruritic manifestations of atopic dermatitis under the supervision of a specialist. Expert opinion should be sought prior to the use of the product in other corticosteroid responsive dermatoses in children.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Flutivate 0.05% kräm, which has been registered in Sweden by GSK since 10 September 1993. In the Netherlands, the product has been registered since 5 October 1993 by GlaxoSmithKline B.V. under the brand name Cutivate crème 0.5 mg/g (NL License RVG 16647). In addition, reference is made to Flutivate and Cutivate authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Czech Republic, Denmark, Finland, Norway, Poland, Sweden and the Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, an hybrid application. As required by article 10(3) a comparative clinical trial needs to be performed to demonstrate therapeutic equivalence, as showing bioequivalence by pharmacokinetics is not possible. A rather rare exception concerns topical glucocorticosteroids, provided that the generic product is qualitatively and quantitatively identical to that of the innovator. In this situation a vasoconstriction assay (VCA) may replace the need for clinical data.
As Fluticasonpropionaat Xiromed 0.5 mg/g cream was shown to be qualitatively and quantitatively identical to the innovator
product, the MAH submitted a VCA to establish ‘bioequivalance’ of the test and the reference product.

II. QUALITY ASPECTS

II.1 Introduction

Fluticasonpropionaat Xiromed 0.5 mg/g cream is a white, viscous and homogenous cream with pH 5.5 and viscosity -- cps . Each gram of cream contains 0.5 mg fluticasone propionate.

The cream is packed in collapsible aluminum tubes internally coated with an epoxyphenolic lacquer and with white high-density polyethylene screw cap.

The excipients are: macrogol cetostearyl ether, cetostearyl alcohol, isopropyl myristate, paraffinum liquidum, purified water, propylene glycol, citric acid monohydrate, disodium phosphate anhydrous and imidurea.

II.2 Drug Substance

The active substance is fluticasone propionate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white powder, which is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in alcohol. There is no indication that different polymorphic forms are formed with the proposed manufacturing procedure.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of the MAH comprises of the Ph. Eur. monograph for this drug substance, the additional tests and limits on the CEP, and tests and limits for microbial purity and particle size distribution. The limits for particle size distribution are in conformity with the particle size distribution values found in the clinical trial/biobatch. Batch analysis data of parameters in the Ph. Eur. and CEP certificate have already been assessed in the CEP procedure.

Stability of drug substance
The active substance is stable for 36 months/years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation development was undertaken on the basis of the study of the innovator product. The following parameters were used to characterise the innovator product and to create a new formulation with similar characteristics: appearance, density, viscosity and pH microscopic evaluation (droplet size and drug substance particle size), assay, degradation products, etc. As it is a topical preparation, the essential similar property is based on the similarity of the formulations, both qualitatively and quantitatively, and the demonstration of therapeutic equivalence by means of clinical/pharmacodynamic studies.
The clinical trial/bio(test) batch used in the clinical/pharmacodynamic studies is acceptable from a quality point of view: the quantitative composition of the batch is similar to the proposed quantitative composition for marketing and the batch is sufficiently large to be representative for the proposed product. Ph. Eur. preservative efficacy of the product has been demonstrated.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is sufficiently described, including the experimental conditions and in-process controls. The process consists of producing of an O/W emulsion from a water phase and oily phase while stirring at elevated temperatures followed by filling of the bulk product into the aluminium tubes.
Adequate process validation studies are submitted of two pilot batches and four production scale batches, demonstrating batch-to-batch consistency on several process parameters and quality attributes throughout the different steps of the process runs, including assay, degradation products, average and uniformity of weight, appearance, viscosity, pH, droplet size, drug substance particle size, microbial purity, etc.

Control of excipients
The excipients comply with the Ph.Eur. except for imidazolinyl urea, which complies with the United States Pharmacopoeia and National Formulation. The specifications are acceptable.

Microbiological attributes
A preservative efficacy has been performed with a development product batch with the same composition as proposed but containing with 90% of the preservative, and, also a test performed after storage of the batch during one year at long term storage conditions, and after storage during six months at 40ºC/75% R.H. The results complied to the Ph. Eur. criteria. The preservative efficacy can be considered sufficiently demonstrated.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, pH, viscosity, average and uniformity of weight, degradation products, microbiological control, particle size and droplet size. The release and shelf-life requirements/limits are identical with the exception of the limit for pH, viscosity, degradation products. The limits are in conformity with the batch release data and stability results. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production batches, from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three production scaled batches stored at 25°C/ 60%RH (up to 36 months), 30°C/65%RH (up to 36 months) and 40°C / 75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. All parameters were well within the proposed specification limits. A photostability study has been performed and the results show that the product is light resistant. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are: “Do not store above 30ºC”. After first opening, the product has a shelf life of 6 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fluticasonpropionaat Xiromed has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. There were no post-approval commitments made during the procedure.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Fluticasonpropionaat Xiromed is intended for substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Flutivate which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fluticasone propionate is a well-known active substance with established efficacy and tolerability. No pharmacokinetics studies were performed to examine equivalence. The MAH performed a pharmacodynamics equivalence study which is discussed below.

IV.2 Pharmacodynamics

The MAH conducted a vasoconstriction assay (VCA) using the test product Fluticasonpropionaat Xiromed 0.5 mg/g cream (Exeltis Healthcare S.L., Spain) and the reference product Flutivate 0.05% kräm (GSK, Sweden) in order to demonstrate therapeutic equivalence. As it concerns a topically applied glucocorticoid, which is both qualitatively and quantitatively similar to the reference product, a vasoconstriction assay may replace the need for clinical data. This is in accordance with the Question and Answer document on the guideline Clinical investigation of corticosteroids intended for use on the skin (CHMP, November 2006). In this document a summary of the testing principles is given referring to a detailed description of how to perform vasoconstriction assays in the FDA's Guidance for Industry "topical dermatologic corticosteroids, in vivo bioequivalence" (June, 1995).

The choice of the reference product
The choice of the reference product in the VCA has been justified by comparison of compositions of reference products in different member states.
The formula and preparation of the batch used in the VCA is identical to the formula proposed for marketing.

Design
The assay was designed as a single-centre, randomized, single-blind, 3-phase, pharmacodynamic bioequivalence study using within-study day replicate single dose durations of test and reference products in 62 healthy subjects. The study consisted of 3 separate phases:
- screening
- pilot phase
- pivotal phase.

Responders in the screening phase i.e. those with a blanching response on reference product applied for 6 hours entered the pilot or pivotal study phase.
Of a total of 157 healthy volunteers 12 subjects entered the pilot phase and 50 subjects in the pivotal phase. In the pilot phase the duration of application of the reference product (approximately q10 mg (4 mcg/cm^2) semi-occlusion) was determined.
In the pivotal phase blanching of the test product was compared to that of the reference product. Test sites were randomly allocated to the right and left ventral forearms including 12 active sites and 4 untreated semi-occlusive control sites.

Duration of the application was 105 minutes. This was the dose-duration that causes 50% of the maximum effect (ED50) determined in the pilot phase. The reference agent was also applied at shorter (52 minutes) and longer dose durations (210 hours) as calibrators in order to ensure the sensitivity of the study. The products and the dose duration were assigned at random to the test zones on the right and left of the anterior of the forearm. Each volunteer received:

- Two applications per arm of the experimental product at ED50,
- Two applications per arm of the reference at ED50,
- One application per arm of the reference in the 52 minutes and 3.5 hours,
- Untreated control zones per arm.

Assessment of skin blanching at each test site was performed using a colorimeter at baseline, 0 h and at approximately 2, 4, 6, 19 and 24 h after product removal.

Primary endpoint

Primary endpoint was the AUEC (0-24) that is area under effect curve 0-24 hours from detachment. Colometric values were baseline-adjusted and corrected for untreated control sites. To be coined as 'detectors' the AUEC(0-24) at for 52 minutes and had to be negative and the ratio in AUEC(0-24) of the 210 and 52 minute application had to be larger than 1.25.

Results

A total of 157 subjects were screened of whom 62 met the entry criteria. Ten subjects entered the pilot phase and a total of 50 subjects were included in the pivotal phase. In the pivotal phase, considering $AUEC_{(0-24)}$ values for D_1 and D_2, subjects were classified as subjects with a full colorimeter profile (detectors) or subjects without a full colorimeter profile. Subjects without a full colorimeter profile were excluded from the analysis of bioequivalence.

Only 19 of the subjects included in the pivotal phase were classed as dectectors and were included in the analysis of bioequivalence. These subjects had 2-arm $AUEC_{(0-24)}$ averages for both D1 and D2 that were negative and they met the dose duration-response criterion of $R_{AUEC} \geq 1.25$.

(AUEC = area under the effect curve, $D_{1=}$ 0.5 times half-maximal dose duration, $D_{2=}$ 2 times half-maximal dose duration, R= reference listed drug at half-maximal effect dose duration).

The means, variances and covariance for the test and reference products Flutivate (both at the ED50 of 1.75 h) are presented below.

Table 1.

$AUEC_{(0-24)}$	**Test**	**Reference**
Mean	-6.62	-6.47
Variance	15.60	20.23
Covariance	14.30	
$CI_{90\%}$	87.2% <> 122.6%	

The applicable acceptance range of 0.80-1.25 for bioequivalence studies was extrapolated to the vasoconstriction assay. This extrapolation was sufficiently justified by the MAH. The 90% confidence intervals calculated for $AUEC_{0-24}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the results of the vasoconstriction assay, Fluticasonpropionaat Xiromed 0.5 mg/g cream is equivalent to the innovator product Flutivate 0.05%.

The study was conducted in accordance with the FDA's Guidance for Industry *Topical dermatologic corticosteroids, in vivo bioequivalence*, issued June, 1995. This is acceptable.

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 Fluticasonpropionaat Xiromed.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Cutaneous atrophy with prolonged use (mainly on the face) - Worsening of psoriatic conditions - Secondary infections - Skin reactions due to excipients (mainly Imidurea) - Systematic effects (Cushing´s syndrome, Cushingoid features, hypercortisolism, Hypothalamic–pituitary–adrenal axis suppression and adrenal suppression)
Important potential risks	- Continuous application on eyelids resulting in cataract and glaucoma
Missing information	- Safety in pregnancy and lactation - Safety and efficacy in paediatric patients below 3 months of age

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Flutivate. No new clinical studies were conducted. The MAH demonstrated through a pharmacodynamics equivalence study that the pharmacodynamic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

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 test was divided into three steps: pilot interviews (5 subjects), first and second sets of interviews (10 participants each). The pilot phase was useful to determine the modifications that would later be introduced in the questionnaire and the leaflet to improve their clarity. Results of the first set of interviews met the success criteria, and those of the second set confirmed the former. The leaflet achieved positive results in the readability test. 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

Fluticasonpropionaat Xiromed 0.5 mg/g cream has a proven chemical-pharmaceutical quality and is a hybrid form of Flutivate 0.05% cream. Flutivate is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence was demonstrated by means of a vasoconstriction assay (VCA) in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fluticasonpropionaat Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 December 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Article 45 or 46 of Regulation (EC) No 1901/2006	NL/H/3524/ 001/IB/001	Type IB: C.I.3.z	03-04-2018	14-05-2018	Approved	No
- Change in the (invented) name of the medicinal product; for Nationally Authorised Products - Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use; Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	NL/H/3524/IB/002/G	Type IB: A.2.b; Type IAin: C.I.8.a	01-09-2018	10-09-2018	Approved	Yes