CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Cortifil 0.5 mg/g cream
Laboratorios SALVAT, S.A., Spain

fluticasone propionate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1295/001/DC
Registration number in the Netherlands: RVG 102106

3 May 2010

Pharmacotherapeutic group:	potent corticosteroids (group III), dermatological preparations
ATC code:	D07AC17
Route of administration:	cutaneous
Therapeutic indication:	inflammatory dermatoses not caused by micro-organisms and responsive to corticosteroids in adults and children aged 1 year and over; relief of the inflammatory and pruritic manifestations of atopic dermatitis in children aged 1 year and over who are unresponsive to lower potency corticosteroids.
Prescription status:	prescription only
Date of authorisation in NL:	2 November 2009
Concerned Member States:	Decentralised procedure with ES, FR, IT, PT, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Cortifil 0.5 mg/g cream, from Laboratorios SALVAT, S.A. The date of authorisation was on 2 November 2009 in the Netherlands.

For adults and children aged 1 year and over, the product is indicated for symptomatic treatment of inflammatory dermatoses not caused by micro-organisms and responsive to corticosteroids such as:

- eczema including atopic and discoid eczemas
- psoriasis (excluding widespread plaque psoriasis)
- lichen planus
- lichen
- contact sensitivity reactions
- discoid lupus erythematosus
- as adjunct to systemic steroid therapy in generalised erythroderma.

For children aged 1 year and over who are unresponsive to lower potency corticosteroids, Cortifil 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 Cortifil in other corticosteroid responsive dermatoses in children.

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

Fluticasone propionate as a glucocorticoid has anti-inflammatory and vasoconstrictive features. Applied topically on the skin it suppresses inflammatory reactions and symptoms although without curing the underlying disorder. Systemic absorption through the subcutaneous tissues is low.

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 medicinal product is a locally applied and local acting drug for which bioequivalence cannot be demonstrated through bioavailability studies. The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, 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 Cortifil 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.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. The current product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted, as this is not required for a hybrid medicinal product.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active 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 Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Fluticasone propionate is prepared in a seven-stage synthesis. The final step of preparation consists of micronisation of the dried active substance. Detailed information on the manufacture is included in the restricted part of the ASMF.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. with additional limits for particle size. Batch analytical data demonstrating compliance with the drug substance specification have been provided for seven pilot-scale batches and three production-scale batches.

Stability of drug substance
The presented stability results were obtained by testing three batches produced following a smaller scaled, 'old' manufacturing procedure, and two batches produced in accordance with the current manufacturing procedure. The three smaller scaled batches were stored at 25°C/60% RH (48 months) and at 40°C/75% RH (6 months). The two batches that were produced in accordance with the current manufacturing procedure, were stored at 25°C/60% RH for 24 months and 12 months respectively.
The results show that none of the tested parameters is susceptible to change during the tested period. No significant differences are noted between the results of the full-scale batches that are produced in accordance with the current manufacturing procedure and the results of the smaller scale batches that were produced in accordance with the old manufacturing procedure. In view of this, it can be concluded that the active substance is stable under both long term and accelerated conditions. The proposed retest period of five years could be granted, with no specific storage conditions.

**Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Cortifil 0.5 mg/g is a white, viscous and homogeneous cream with pH 4.5-6.0 and viscosity 45,000-70,000 cps.

The cream is packed in aluminium tubes with a white high-density polypropylene screw cap. The tubes are filled with 30 g of cream.

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

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. 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 excipients used are common in cutaneous dosage forms. The quantities used are common as well. No overage is applied.
The MAH provided sufficient information on the two release/permeation studies conducted prior to the clinical trial. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
A flow chart and a description of the manufacturing process including in-process control were included. Sufficient information has been provided. The production of an emulsion is considered a non-standard manufacturing process. Validation data have been provided on a total of three production-scale batches. The process has been adequately validated.

Control of excipients
The excipients comply with the Ph.Eur. except for imidazolinyl urea, which complies with the USP/NF. These specifications are acceptable.

Container closure system
The product is packed in aluminium tubes with an external white polyester transpiring enamel, a gold epoxy-phenolic internal varnish and a water based sealing compound for aluminium collapsible tubes. The authorised texts are printed on the exterior of the tube. The tube is closed with a white, HDPE screw cap. Each tube contains 30 g of cream. The stability studies of the medicinal product confirm the compatibility of the formula with the primary packing material. The results show that there is no interaction between the cream and the tube's components that affect the quality of the product. The provided information is regarded to be sufficient.

Quality control of drug product
The product specification includes tests for appearance, identity, pH, viscosity, uniformity of weight, assay, degradation products, microbiological control, particle size and droplet size. In case of the viscosity, pH and degradation products, the release and shelf-life limits are not identical. The applied limits are acceptable. The MAH committed to re-evaluate the shelf-life limits when more experience has been gained with sufficient production batches.
For particle size, which can control permeation rate, and droplet size (to ensure absence of agglomeration), appropriate limits have been established. Batch analytical data have been provided on two pilot-scale batches and one production-scale batch. In addition, process validation data including release data of three production batches were presented. The batches comply with the specification.

Stability of drug product
Two pilot-scale batches were stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and at 40°C/75% RH (6 months). For one production-scale batch, 12 months data at 25°C/60% RH are available, as well as 12 months at 30°C/65% RH and 6 months at 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. Aluminium tubes were used as packaging material. For none of the batches tested a significant change is observed, except regarding viscosity at accelerated conditions. The product remained stable in the proposed package for the duration of the studied period.

Based on the currently available data, the proposed shelf-life of 36 months, when stored below 30°C, is acceptable. An in-use stability test conducted over 6 months demonstrated that the product remains stable under normal conditions of use during this period.
The photostability test, performed in accordance with the ICH testing conditions, concludes that the product is not sensitive to light.
Two post-approval commitments have been made regarding the stability studies, which can be found on page 8 of this report.

Microbiological attributes
In order to prevent contamination of the product, imidurea (imidazolinyl urea), a well-known preservative has been added to the formula at a concentration of 0.2%. An efficacy study was conducted following the acceptance criteria established by the Ph. Eur. (5.1.3.) for topical preparations, the result complying. Supplementary efficacy tests were also conducted during development on samples exposed to 40ºC/75% RH for 6 months and on samples with 90% of the preservative (i.e. 0.18%, which is the minimum concentration specified for Imidurea at the end of the shelf-life of the drug product). The results of the tests were acceptable. The microbiological quality is adequately controlled.

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.2 Non clinical aspects

This active substance has been available on the European market for more than 10 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of fluticasone propionate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Fluticasone propionate is a well-known active substance with established efficacy and tolerability.

For this hybrid application, the MAH has submitted a vasoconstriction assay (VCA) using the test product Cortifil 0.5 mg/g cream and the reference product Flutivate 0.05% 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, Cortifil 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.

Risk management plan

Fluticasone was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of fluticasone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Pharmacovigilance system

The MAH committed to ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Product information

SPC

The content of the SPC was adequately adapted in accordance with the member states' comments. In some member states, the innovator product is approved for use in children from the age of 3 months. For approval of the use in children aged 3 months-1 year, a type II variation would be needed.

Readability test

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 report on the readability test clearly reflects the performance of the tests, the results and the conclusions based on the results. The test consisted of a pilot test, followed by two rounds with 10 participants each. Twelve questions were asked. Overall, each and every question met the criterion of 81% correct answers.

The report ensures that the proposed leaflet reflects the results of the testing with test persons to make sure it meets their needs and can enable a patient to use the medicinal product safely and effectively. Problems regarding comprehensibility have been identified and solved.

The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Cortifil 0.5 mg/g cream has a proven chemical-pharmaceutical quality and is a hybrid form of Flutivate 0.05% cream. Flutivate 0.05% 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 SPC, package leaflet and labelling are in the agreed templates and are in agreement with other fluticasone propionate containing products.

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 Cortifil 0.5 mg/g cream with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 7 June 2009. Cortifil 0.5 mg/g cream was authorised in the Netherlands on 2 November 2009.

A European harmonised birth date has been allocated (8 March 1990) and subsequently the first data lock point for fluticasone is February 2012. The first PSUR will cover the period from June 2009 to February 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 October 2012.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform stability studies with three additional production batches, regarding all parameters as indicated in the stability protocol and to submit the results.
- The MAH committed to provide the results of the ongoing stability studies up to the approved shelf-life when these have been completed. The results of particle size and droplet size should also be included.
- The MAH committed to re-evaluate the shelf-life specification limits according to the stability results of production batches (e.g. regarding pH and viscosity).

Pharmacovigilance system

- The MAH committed to ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
AUEC	Area Under the Effect Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
VCA	Vasoconstriction Assay

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