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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Hydrocortison-vaselinecrème 1% FNA, cream 10 mg/g TioFarma b.v., the Netherlands

hydrocortisone acetate

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 33923

25 August 2010

Pharmacotherapeutic group:	corticosteroids, weak (group I)
ATC code:	D07AA02
Route of administration:	cutaneous
Therapeutic indication:	superficial skin conditions not caused by microorganisms and susceptible to corticosteroids
Prescription status:	prescription only
Date of authorisation in NL:	28 March 2008
Application type/legal basis:	Directive 2001/83/EC, Article 10a

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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Hydrocortison-vaselinecrème 1% FNA, cream 10 mg/g from TioFarma b.v. The date of authorisation was on 28 March 2008 in the Netherlands.

The product is indicated for treatment of superficial skin conditions not caused by microorganisms and susceptible to corticosteroids, such as:
- eczema (dermatitis) of various origin (atopic eczema, orthoergic contact dermatitis, Seborrhoeic dermatitis, varicose eczema)
- localised forms of pruritus (*e.g.* pruritus ani)
- localised forms of prurigo
- some cases of chronic discoid lupus erythematosus (CDLE).

The product is also indicated for continuation or maintenance treatment of dermatoses after successful suppression with a stronger medicinal product.

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

Hydrocortisone is a mild, topical corticosteroid. *In vivo,* its level is regulated by the Hypothalamic-Pituitary-Adrenal (HPA) axis. The molecular mechanism of action of hydrocortisone is similar to that of glucocorticoids in general, and it is mainly receptor binding mediated. Hydrocortisone acetate is classified as a low potency glucocorticoid independent of the cream-base used whether it is a cream, an ointment, or a fatty cream.

This national procedure concerns a so-called bibliographical application in accordance with article 10a of Directive 2001/83/EC. The product at issue concerns a cream. The active substance is hydrocortisone acetate. Hydrocortison-vaselinecrème 1% is a well-known drug product of which the composition is laid down in the Formularium der Nederlandse Apothekers (FNA) since 1989.

This application concerns a bibliographical application based on well-established medicinal use of hydrocortisone cream. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ''Medicinal use'' does not exclusively mean ''use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as no such plan is required for a bibliographical application.

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 hydrocortisone acetate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Hydrocortisone is a white, crystalline powder which is practically insoluble in water.

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 new 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 active substance specification is considered adequate to control the quality and meets the requirements of the CEP and the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance
A retest period of 3 years is applicable when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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
Hydrocortison-vaselinecrème 1% FNA, contains as active substance 10 mg of hydrocortisone acetate per gram, and is a white to off-white cream.

The cream is packed in a 30 mg coated aluminium tube with polypropylene cap.

The excipients are: white vaseline, liquid paraffin (E905), cetomacrogol emulsifying wax, propylene glycol (E1520), purified water.

Pharmaceutical development
The development is adequately described in accordance with the relevant European guidelines. The excipients are well-known in dermal preparations in general. The formulation is based on the FNA formulation 'Hydrocortisonvaselinecrème 1% crème'; the main difference is that in the proposed formulation hydrocortisone acetate is suspended in the fatty (lipophilic) phase. The process is straightforward. The coated aluminium tubes are recommended by FNA. The pharmaceutical development has been sufficiently performed and explained.

Manufacturing process
The manufacturing process has been adequately described. Critical steps and in-process controls were indicated and validated. Tests on homogeneity of the final cream in filled tubes and weight of content of filled tubes are included.
Three batches have been validated showing compliance with the validation requirements. Herewith it has been sufficiently demonstrated that the manufacturing process is under control inside and between batches.

Microbiological attributes
The finished product is tested for microbiological impurities according to the Ph.Eur. In addition, it is stated that hydrocortisone acetate has some antibacterial properties and propylene glycol at the concentration used has anti-microbiological properties and is usually used as preservative in dermatologicals.
Results from the Ph. Eur. test of antimicrobial preservation are included. These results demonstrate that the preservation is adequate at the preservative concentrations as defined by release and shelf-life specification for propylene glycol content. The method used is validated against the Ph.Eur. method.

Control of excipients
The specifications of the excipients are acceptable: all excipients are of compendial quality. Batch analysis certificates were provided.

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, identification, assay, related substances, microbial contamination, particle size and minimum fill. According to the NfG on inclusion of antioxidants and antimicrobial preservatives in medicinal products an identification test and limits for the preservative should be present in the release and end of shelf life specification. An identification test for propylene glycol is present in the release and end of shelf life specification. The analytical methods have been adequately described and validated.
Batch analytical data from 3 production-scale batches have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 production-scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The product was packed in aluminium tubes with PP closure. The total impurities increase during the stability studies at accelerated and long term storage conditions. No photostability test has been performed, since the finished product is stored and delivered in an aluminium tube which prevents any contact of the cream with light. Based on the results, a shelf life of 18 months could be granted. The product should be stored below 25°C.

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 many 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 hydrocortisone 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

Hydrocortisone is a well-known active substance with established efficacy and tolerability.
For this bibliographical application, the MAH has submitted an overview of literature in support of the well-established use of hydrocortisone acetate 1% cream.

Introduction
The clinical/pathophysiological condition that the medicinal product intends to treat is superficial dermatoses such as eczema, psoriasis, contact and atopic dermatitis, itching caused by perianal disorders and all other steroid responsive skin diseases. The inflamed disorders are often accompanied by erythema, pruritus, crusting, and exudation. The discomfort caused by these last symptoms may be suppressed by corticosteroids.
The scientific background that supports the medicinal product is based on the fact that patients showed benefits of a glucocorticoid in the management of the several dermatoses above listed. Glucocorticoids such as hydrocortisone acetate to the cream decrease the inflammation of the skin. In this way, the discomfort such as pruritus, is often resolved. The fact that steroids might lead to bacterial or fungal overgrowth in patients, is less relevant in the case of a short-term therapy.
A similar product to the present formulation is already commercialised in the Netherlands as a safe and effective “De Magistrale Bereider” medicine.
For this reason, the clinical development program of the medicinal product is based on clinical trials described in literature. No clinical studies (efficacy, safety, or clinical bioequivalence) were carried out by the applicant or submitted in this application since scientific literature provides enough arguments to support the efficacy and safety of the medicine. Moreover, similar products (creams, fatty cream, and ointment) are already registered.

Clinical pharmacology
Studies on pharmacokinetics and pharmacodynamics of hydrocortisone acetate 1% in a fatty cream as the present formulation are not available in literature. Therefore, studies on the clinical pharmacology of the active component were discussed, *i.e.* hydrocortisone acetate in preparations for topical use, as creams and ointments in general. The proposed medicine is for topical use during a short-term. Hydrocortisone acetate is a low potency corticosteroid, and the component is known to be percutaneously hardly absorbed (about 1% of the applied dose in case of an intact skin). The clinical overview refers to a number of studies on the bioavailability of hydrocortisone.

Clinical efficacy
The proposed formulation contains hydrocortisone acetate as active component in the form of a fatty cream. Relevant clinical trials on the management of inflammatory skin disorders were described. The efficacy of the products studied is similar depending on the severity of the disorder. Also, the broad age range of the patients enrolled demonstrates that efficacy of the cream is obtained in all age groups. However, the prophylactic management of the disorders may be different among groups. The studies presented and discussed cover different treatment periods and follow-ups. In the case of the present formulation, the treatment term is advised to be about 2 weeks. However, depending on the sort and severity of the disorder the treatment may be prolonged under the supervision of the clinician.

Reference is made to a randomised, double blind bilateral design clinical trial by Kuokkanen and Sillantaka (1987), studying the efficacy and safety of alclometasone dipropionate 0.05% and hydrocortisone 1% ointments in 37 children (37 enrolled, 34 completed the study). Caucasian children (2 – 10 years) with eczema were enrolled the study. Bilateral, symmetrical eczematous lesions on the arms, legs and torso were selected as paired test sites in each patient. The sites had to show similar degree of lesion severity and stability for at least one week prior to treatment. Treatment consisted of application of the ointments twice daily during 3 weeks. Efficacy and safety assessment was performed at the end of each treatment week by monitoring. During the 3 weeks of treatment none of the ointments induced skin atrophy in this population. One patient reported a mildly severe urticarial rash, no treatment was required. After the first and second week of treatment alclomethasone dipropionate 0.05% ointment showed to be superior to hydrocortisone 1% (54% and 71% versus 49% and 67% after week 1 and 2 for alclometasone

and hydrocortisone, respectively). By the end of the third week no significant differences were detected between drugs. The authors concluded that both corticosteroids are comparable in their efficacy and safety.

Another aspect that accounts for the efficacy is the vehicle used in the formulation. In fact, the penetration of the corticosteroid depends on the cream base used. The vehicle may enhance the penetration degree of the drug through the barrier zone of the stratum corneum. Polano and Ponec (1976) already referred to this issue. In their article they reported the effect of propylene glycol in the vehicle on the steroid penetration. They compared the penetration of hydrocortisone butyrate 0.1% in diverse bases, O/W, W/O, and Plastibase (petrolatum with polyetylene) with or without propylene glycol 9%. Cetomacrogol 1000 was used as emulgator since propylene glycol is not miscible in the base. The maximum penetration rates for [14C]PG and hydrocortisone butyrate coincide in time suggesting that they penetrate together. The use of an emulgator together with propylene glycol showed the greatest penetration rates. Also in a clinical trial enrolling psoriatic patients, the therapeutic activity of hydrocortisone butyrate was greater when applied in a base containing propylene glycol. The authors also showed that hydrocortisone penetrates poorly from a greasy base without propylene glycol.

Controversially to those observations, Refai and colleagues (2002) have shown that the base of the cream does not affect significantly the absorption of hydrocortisone *in vitro* and through the excised stratum corneum of human volunteers. Only the presence of an enhancer augments the permeation. When the enhancer is diluted the permeation is reduced. This was also observed for propylene glycol by Polano and Polec (1976).
Altogether, when conclusions and/or extrapolations to the *in vivo* situation are made it should be taken into account that the absorption of a drug is influence by other factors not present in an *in vitro* study. Moreover, the characteristics of base of the formulation are essential.

In conclusion, the proposed product for the treatment of inflamed dermatoses presents a good efficacy. Since hydrocortisone offers a palliative therapy, it may deteriorate lesions with secondary bacterial and fungal infections. For this reason is important to confine the therapy to a short-term.

Clinical safety
Adverse reactions reported after topical use of hydrocortisone are mostly contact dermatitis with pruritus and erythema and skin atrophy. These adverse reactions are mostly due to previous sensitisation to the component and are reversible after discontinuation of the therapy. Also, adverse reactions caused by the vehicle may be present.
Studies of case reports, and/or other studies particularly on the safety of hydrocortisone acetate are discussed in the overview. In addition, a few studies on the safety of components of the vehicle are included.
Safety findings at preclinical and clinical levels related to response of hydrocortisone cream at the same strength and dose prescribed, suggest a good safety profile. The hydrocortisone acetate present in the cream is hardly systemically absorbed and consequently almost no systemic adverse side effects are expected to be related to the product. Concerning hydrocortisone acetate, a low potent glucocorticoid, the HPA axis suppression by this cream is not expected in adults, during a short-term therapy without occlusion. In children this may represent a complication unless the skin surface area is limited and not extensively used in skin folds (axilae, diaper region, and groin). Under those circumstances the formulation is also considered to be safe.
The adverse events reported are predominantly contact dermatitis. In a large number of the cases, the reaction is due not only hydrocortisone acetate but to the vehicle. In fact, the presence of a vehicle which enhances the bioavailability of the drugs may initiate the cascade of dermatological adverse reactions. Also, vehicle components such as propylene glycol may itself cause side effects. However, the risk of adverse events is confined to sensitive persons.
Persons consuming food, using hygienic products/cosmetics, or other medicines containing propylene glycol should be aware of the possibility to develop adverse skin reactions, such as irritation or contact dermatitis. Those reactions may be a consequence of a previous sensitisation to propylene glycol. No other interaction with food or other drugs are expected to take place during the topical therapy.

When analysing the benefit/risk ratio, in the case of a topical product such as hydrocortisone acetate 1% fatty cream, which is widely prescribed, the side effects reported are rare.

Risk management plan

Hydrocortisone vaselin cream is an established product, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of hydrocortisone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with that accepted for other established hydrocortisone creams. The SPC has been adequately adapted in accordance with the MEB's comments.

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 test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Hydrocortison-vaselinecrème 1% FNA, cream 10 mg/g has a proven chemical-pharmaceutical quality and is a well-established medicinal product. Its composition is laid down in the Formularium der Nederlandse Apothekers (FNA) since 1989. Based on the submitted dossier and further literature, Hydrocortison-vaselinecrème 1% FNA can be considered effective in the treatment of superficial skin conditions not caused by microorganisms and susceptible to corticosteroids.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other hydrocortisone containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered well-established medicinal use sufficiently demonstrated, and has therefore granted a marketing authorisation. Hydrocortison-vaselinecrème 1% FNA, cream 10 mg/g was authorised in the Netherlands on 28 March 2008.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CDLE	Chronic Discoid Lupus Erythematosus
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
FNA	Formularium der Nederlandse Apothekers
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

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