

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Triamcinolon-vaseline crème form 0.1% FNA, cream 1 mg/g
TioFarma b.v., the Netherlands**

triamcinolone acetonide

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 33941

12 November 2012

Pharmacotherapeutic group:	corticosteroids, moderately potent (group II)
ATC code:	D07AB09
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:	16 November 2007
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 Triamcinolon-vaseline crème 0.1% FNA, cream 1 mg/g from Tiofarma b.v. The date of authorisation was on 16 November 2007 in the Netherlands.

The product is indicated for superficial skin conditions not caused by microorganisms and susceptible to corticosteroids, such as:

- Psoriasis (vulgaris)
- Lichenification
- Lichen planus
- Lichen sclerosus et atrophicus
- Granuloma annulare
- Lupus erythematosus discoides
- Pustulosis palmaris et plantaris (Andrews-Barber disease)
- Mycosis fungoides.

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

Triamcinolone is a potent dermal corticosteroid with anti-inflammatory and vasoconstrictive activity. It suppresses inflammation and relieves symptoms of itchy skin conditions.

This national procedure concerns a so-called bibliographical application in accordance with article 10a of Directive 2001/83/EC. The active substance is triamcinolone. Triamcinolon-vaselinecrème is a well-known drug product of which the composition is laid down in the Formularium der Nederlandse Apothekers (FNA).

This application concerns a bibliographical application based on well-established medicinal use of triamcinolone 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 triamcinolone acetonide, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white to off-white crystalline powder, which is soluble in alcohol and chloroform, and 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 for 3 batches.

Stability of drug substance

Stability data on the active substance have been provided for 4 batches stored at 25°C/60%RH (60 to 72 months). All results complied with the set specifications. Based on the results, a retest period of 5 years has been granted.

* *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

Triamcinolon-vaseline crème is a white fatty cream, containing 1 mg/g of triamcinolone acetonide.

The cream is packed in aluminium tubes with polypropylene closures.

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

Pharmaceutical development

The formulation and compounding is basically that of 'Triamcinolonacetonidevaselinecreme 0.1%' described in the Dutch Formularium der Nederlandse Apothekers'(FNA). It is indicated that the only difference is that in the proposed process the triamcinolonacetonide (TCA) is suspended in the fatty phase and not dissolved in propylene glycol. In fact, in the current description of the manufacture in FNA TCA is not dissolved in propylene glycol but dispensed in a small amount of propylene glycol.

In a study the MAH has manufactured the product according to the proposed method and according to the method described in the FNA and compared both products. The following was observed: that both creams have the same physical characteristics (appearance, spreadability), and no differences could be found between the creams concerning the particle size and distribution when analysed under microscope. Literature has been provided to justify that always the same form will be present in each TCA cream that contains water. Moreover, the FNA specifications for particle size have been adopted and followed in the on-going stability study.

The presence of propylene glycol at 10% in the cream should result in acceptable preservative efficacy. Results have been provided of testing Ph Eur 'Efficacy of antimicrobial preservation' which demonstrate compliance with criteria A for three of the tested organisms and compliance with criteria B for *A. Niger*. The preservative activity is considered acceptable.

Manufacturing process

The manufacturing process has been adequately described. Control of critical steps and intermediates are included. Information about the test methods and applicable limits of the IPCs has been given. Results of process validation of three production-scale batches have been provided.

Control of excipients

The specifications of the excipients are acceptable.

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 (triamcinolone acetonide and propylene glycol), assay, related substances, microbiological purity, particle size and minimum fill. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The analytical methods have been adequately described and validated.

Batch analytical data from three 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 batches during storage at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The stability results show that no trends are observed and all results comply. Based on the data provided, a shelf life of 24 months can be granted, when stored below 30°C as proposed by the MAH.

The MAH has provided only results covering one month in-use storage. Therefore an in-use shelf life of only 1 month was granted.

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. 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 MEB agreed that no further non-clinical studies are required.

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 triamcinolone acetonide 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

Triamcinolone acetonide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agreed that no further clinical studies are required.

Risk management plan

Triamcinolone acetonide cream is an established product, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of triamcinolone acetonide 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. 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 those accepted for other triamcinolone acetonide creams.

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 a pilot test, followed by two rounds with 10 participants each. Fifteen questions were asked. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question meets criterion of 81% correct answers. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Triamcinolon-vaseline crème 0.1% FNA, cream 1 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). Based on the submitted dossier and further literature, Triamcinolon-vaseline crème 0.1% 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 triamcinolone acetonide 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. Triamcinolon-vaseline crème 0.1% FNA, cream 1 mg/g was authorised in the Netherlands on 16 November 2007.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to provide stability results covering the whole shelf life when available.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the 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 _{1/2}	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
Addition of a manufacturer of the active substance	--	IA	11-11-2009		Approval	N