CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Acitretine Genus Pharmaceuticals 10 mg and 25 mg, capsules
Genus Pharmaceuticals Ltd., United Kingdom

acitretin

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/1959/001-002/DC
Registration number in the Netherlands: RVG 107065-107066

9 May 2011

Pharmacotherapeutic group:	retinoids for treatment of psoriasis
ATC code:	D05BB02
Route of administration:	oral
Therapeutic indication:	psoriasis; ichtohyosis and ichthyosiform dermatitis; lichen ruber planus; dermatitis characterised by dyskeratosis and/or hyperkeratosis
Prescription status:	prescription only
Date of authorisation in NL:	17 March 2011
Concerned Member States:	Decentralised procedure with UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 Acitretine Genus Pharmaceuticals 10 and 25 mg, capsules from Genus Pharmaceuticals Ltd. The date of authorisation was on 17 March 2011 in the Netherlands.

The product is indicated for:
- Extensive and severe refractory forms of psoriasis;
- Pustulous psoriasis of the hands and feet;
- Severe congenital ichthyosis and ichthyosiform dermatitis;
- Lichen ruber planus of skin and mucous membranes;
- Other severe and refractory forms of dermatitis characterised by dyskeratosis and/or hyperkeratosis.

Actitretine Genus Pharmaceuticals should only be prescribed by doctors, preferably dermatologists, who have experience in treatment with systemic retinoids and correctly estimate the teratogenic risk posed by acitretin.
A comprehensive description of the indications and posology is given in the SPC.

Retinol (Vitamin A) is known to be essential for normal epithelial growth and differentiation, though the mode of this effect is not yet established. Both retinol and retinoic acid are capable of reversing hyperkeratotic and metaplastic skin changes. However, these effects are generally only obtained at dosages associated with considerable local or systemic toxicity.
Acitretin, the active ingredient of Actitretine Genus Pharmaceuticals, is a synthetic aromatic analogue of retinoic acid and the main metabolite of etretinate, which has been used with success for a number of years in the treatment of psoriasis and other disorders of keratinisation.
Clinical studies have confirmed that, in psoriasis and dyskeratosis, acitretin brings about a normalisation of epidermal cell proliferation, differentiation and keratinisation in doses at which the side effects are generally tolerable. The effect of acitretin is purely symptomatic: the mechanism of action is still largely unknown.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Soriatane 10 mg capsules which has originally been registered by Roche on 12 September 1988. The licence was later transferred to Actavis Group PTC ehf, Iceland. In the Netherlands, the innovator product has been registered since 26 October 1989 under the brand name Neotigason 10 mg and 25 mg capsules (NL License RVG 13103-13104). In addition, reference is made to Soriatane/Neotigason authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the 25 mg product is compared with the pharmacokinetic profile of the reference product Soriatane 25 mg capsules, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

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 this is not required for a generic 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 these product types 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 acitretin, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a yellow or greenish-yellow crystalline powder, which is practically insoluble in water and slightly soluble in acetone. Acitretin exhibits polymorphism.

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 drug substance specification is in line with the Ph.Eur. and the CEP. The specification is acceptable in view of the various European guidelines. Batch analytical data have been provided for 4 batches demonstrating compliance with the specification. Information on the polymorphic form was requested. The consistent polymorphic form is guaranteed.

Stability of drug substance
The stability of acitretin has been assessed by the EDQM, and a re-test period of 5 years is assigned if stored in the packaging material as specified on the CEP.

** 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
Actitretine Genus Pharmaceuticals 10 mg consists of a white to off-white body and a brown cap, printed in black with “A10” on the capsule body and filled with a yellow powder.
Actitretine Genus Pharmaceuticals 25 mg consists of a yellow to light yellow body and a brown cap, printed in black with “A25” on the capsule body and filled with a yellow powder.

The capsules are packed in PVC/PVDC aluminium blister packs.

The excipients are:
Capsule filling - maltodextrin, sodium ascorbate, microcrystalline cellulose
Capsule shell – gelatin, sodium laurilsulfate, titanium dioxide (E171), iron oxide yellow (E172), iron oxide black (E172), iron oxide red (E172), shellac.
The two strengths are dose-proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development studies are briefly described. The process of making the final choice of the proposed composition has been clearly explained.
The proposed products have been compared with originator products. The drug substance is poorly soluble in buffer media. The batch used for the 25 mg dissolution study is the one used in the bioequivalence studies. The dissolution profiles are similar between the originator and the proposed products. For the 25 mg tablet bioequivalence studies have been performed with the corresponding reference product from the French market. This test product is acceptable as the reference product has an identical composition as the NL product.
The pharmaceutical development has been satisfactory described.

Manufacturing process
The drug products are manufactured by a spray-drying process. A suspension is granulated by spray-drying. The granules are then blended and filled into capsules. Validation has been performed on four common blend batches and two commercial-scale batches of each strength. The manufacturing process is considered adequately validated for an acceptable batch size. Further process validation on commercial-scale batches will be performed post approval.

Control of excipients
Except for the colouring agents and the printing ink, where an in house specification is provided, all other excipients comply with their Ph.Eur. monograph. These specifications are acceptable.

Quality control of drug product
The finished product specification is in general regarded acceptable taking into account all important parameters of the product. The specification includes tests for description, length, width, identification, assay, uniformity of dosage units, related substances, dissolution and microbial limits.
All analytical methods have been adequately described and the quantitative methods have been adequately validated. The stability indicating nature of the assay methods have been demonstrated. Batch analysis results are provided for three batches of both strengths of the capsules, demonstrating compliance with the release specifications.

Stability of drug product
Stability data have been provided on drug product stored at 25°C/60% RH (up to 24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). All parameters remained well within limits. No clear trends could be observed. Based on the results of the photostability study it can be concluded that there is practically no change observed in the 10 mg and 25 mg capsules following direct exposure to light.
For both capsule strengths the claimed shelf life of 2 years is justified. With storage condition; ‘Do not store above 30 °C, and store in original packaging to protect the product from moisture’.
A commitment was made that, if a batch is discovered at the lower limit of sodium ascorbate, this product batch will be placed on stability testing over the proposed shelf life at 25 °C/60% RH and for 12 months at 30 °C/65% RH.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin sources used in the manufacture of the capsules are of bovine origin. The TSE Certificate of Suitability from the supplier of bovine gelatin is provided and confirms the acceptability of the material used.

II.2 Non-clinical aspects

This product is a generic formulation of Neotigason, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 acitretin 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Actitretine Genus Pharmaceuticals 25 mg capsules (Genus Pharmaceuticals Ltd., United Kingdom) is compared with the pharmacokinetic profile of the reference product Soriatane 25 mg capsules (Roche, France).

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

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 40 healthy male subjects, aged 18-53 years.
Following an overnight fast, subjects consumed a standardised high-fat breakfast prior to drug administration.
Each subject received a single dose (25 mg) of one of the 2 acitretin formulations. The tablet was orally administered with 240 ml water within minutes of consuming breakfast over a 30 minute period prior to dosing. There were 2 dosing periods, separated by a washout period of 4 weeks.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5,4, 4.5, 5, 5.5, 6, 7, 9, 12, 16, 20, 24, 32, 48, 72, 96, 120, 144, 216, 264 and 312 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject withdrew from the study for personal reasons. Phamacokinetic and statistical analyses were performed on the 39 subjects that completed the study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of trans-acitretin under fed conditions.

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1579.2 ± 539.5	1605.9 ± 541.8	289.1± 81.2	4.7 (2.5 – 6)	3.2 ± 0.9
Reference	1491.5 ± 520.8	1516.3 ± 524.0	280.8 ± 83.8	4.6 (1.5 – 6)	3.2 ± 0.9
***Ratio (90% CI)**	1.01 (1.00 – 1.11)	1.01 (1.01 – 1.11)	1.00 (0.98–1.07)	--	--
CV (%)	13.2	12.9	11.1	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity				
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours				
C_{max}	maximum plasma concentration				
t_{max}	time for maximum concentration				
$t_{1/2}$	half-life				

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of acitretin under fed conditions, it can be concluded that Actitretine Genus Pharmaceuticals 25 mg and Soriatane 25 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Acitretin is recommended to be taken with food. Bioavailability of a single dose is approximately 60% after food, but inter-patient variability is considerable (36 - 95%). The bioequivalence study under fed conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to 10 mg capsule
The 10 and 25 mg capsules are dose-proportional. The capsules have been manufactured by the same manufacturing process. In addition, acitretin shows linear pharmacokinetics in the recommended dosing range. Dissolution results were also demonstrated to be comparable. The results obtained with the 25 mg capsules therefore apply to the 10 mg strength as well.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Acitretin was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of acitretin can be considered to be well established. However, for acitretin strict risk minimisation measures have been laid down regarding pregnancy prevention. The MAH will at least follow the innovator pregnancy prevention programme (PPP) or the EU PPP for isotretinoin, another vitamin A derivative. A monitoring system for pregnant women and congenital malformations should be in place. The MAH will submit the PPP for assessment and discussion to all national competent authorities before placing the product on the market.

Product information

SPC
There was some discussion during the procedure with regard to the indication and contraindication, as the innovator registration has not been harmonised between member states. Agreement was reached which was acceptable for all member states.

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. Sixteen questions were asked. There was a sufficient number of open questions covering the key items. The answers were rated based on whether the information could be found, was understandable, whether subjects could locate it easily and would be able to act upon it.
The results demonstrated that the PIL meets the readability criteria. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Actitretine Genus Pharmaceuticals 10 mg and 25 mg, capsules have a proven chemical-pharmaceutical quality and are generic forms of Neotigason 10 mg and 25 mg. Neotigason is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be 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 acitretin 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 Actitretine Genus Pharmaceuticals 10 mg and 25 mg, capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 February 2011. Actitretine Genus Pharmaceuticals 10 mg and 25 mg, capsules were authorised in the Netherlands on 17 March 2011.

A European harmonised birth date has been allocated (1 December 1987) and subsequently the first data lock point for acitretin is October 2012. The first PSUR will cover the period from February 2011 to October 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: October 2015.

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

Quality - medicinal product

- The MAH committed to perform process validation on 3 commercial-scale batches of 10 mg capsules and 5 commercial-scale batches of 25 mg capsules (at different batch sizes)
- The MAH committed that, if a batch is discovered at the lower limit of sodium ascorbate, this product batch will be placed on stability testing over the proposed shelf life at 25 °C/60% RH and for 12 months at 30 °C/65% RH.

Pharmacovigilance system

- The MAH committed to submit the PPP for assessment and discussion to all national competent authorities before placing the product on the market.

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
PPP	Pregnancy Prevention Programme
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