COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Alizem 10 mg and 30 mg soft capsules

(alitretinoin)

NL/H/4058/001-002/DC

Date: 3 May 2019

This module reflects the scientific discussion for the approval of Alizem 10 mg and 30 mg soft capsules. The procedure was finalised at 20 December 2018. 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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 Alizem 10 mg and 30 mg soft capsules from Pierre Fabre Benelux N.V.

The product is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.

Patients in whom the eczema has predominantly hyperkeratotic features are more likely to respond to treatment than in those in whom the eczema predominantly presents as pompholyx (see SmPC section 5.1).

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Toctino 10 and 30 mg capsules which has been registered in Denmark by Stiefel Laboratories (Ireland) Ltd since 17 September 2008 (original product). In the Netherlands, Toctino (NL Licence RVG 100957 and 100962) has been registered since 14 April 2009 by the procedure DK/H/1377/001-002.

The concerned member state (CMS) involved in this procedure was France.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Alizem is an oval, soft, gelatin capsule, containing a yellow to orange, opaque, viscous suspension:

- 10 mg capsules are light brown capsules.
- 30 mg capsules are yellow capsules

And contains as active substance 10 mg or 30 mg of alitretinoin.

The soft capsule is packed in PVC/PVDC/Aluminium blister.

The excipients are:
Capsule content – refined soya-bean oil, partially hydrogenated soya-bean oil, hydrogenated vegetable oil, glycerol monostearate, medium chain triglycerides, all-rac-α-tocopherol

Capsule-shell – gelatin, glycerol, liquid (non-crystallising) sorbitol (E420), titanium dioxide (E171), water purified, red iron oxide (E172) (10 mg capsule), yellow iron oxide (E172), black iron oxide (E172) (10 mg capsule)

The capsule content of the two tablet strengths is dose proportional.

II.2 Drug Substance

The active substance is alitretinoin, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). It is a yellow to orange crystalline powder. The drug substance has poor solubility in aqueous media. Alitretinoin is an achiral molecule. It is non hygroscopic. There are no stereo centres. The manufacturing process constantly results in the same crystalline form.

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/EMA 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

Alitretinoin is manufactured in three steps. The description of the process is considered adequate.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the ICH guidelines and the Ph.Eur. (microbiological tests). Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. Based on the data submitted, a retest period could be granted of 12 months. It is recommended to store alitretinoin in well closed container protected from oxygen and light at a mean temperature of 25°C with allowed excursions at 15-30°C. It is recommended that the content of an opened container is used as soon as possible and any unused part should be protected under vacuum or under atmosphere of an inert gas.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained.

Bioequivalence studies have been executed with both strengths 10 mg and 30 mg. Comparative dissolution data to support bioequivalence has been provided, according to the conditions as per Guideline on investigation of bioequivalence.
The dissolution method has been justified and the discriminatory power of the dissolution method has been demonstrated.

Manufacturing process

The manufacturing process is considered not standard as the capsules contain a suspension. The description of the manufacturing process has been clearly described.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two batches of each strength in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with Ph.Eur. requirements, except soya bean oil, partially hydrogenated which complies with DAB. These specifications 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 description, capsule dimensions, identification, assay of alitretinoin and alpha-tocopherol, uniformity of dosage units, hardness, related substances, dissolution, and microbiological quality.
Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

The conditions used in the stability studies are according to the ICH stability guideline. Long-term stability data up to 18 months have been provided. The results of the stability data are within the specifications and no specific trends are observed. The data support the proposed shelf-life of 24 months, without any special storage conditions. On basis of the data submitted, a shelf life was granted of 24 months without special storage conditions.
Photostability testing was performed on one batch each of Alitretinoin strength in accordance with ICH guidelines. No change was observed after exposure to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Gelatin is the only material of animal or human origin included in the drug product. Adequate data has been provided to support the TSE safety of this excipient.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Alizem has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Alizem is intended for generic 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 generic formulation of Toctino 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

Alitretinoin 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Alizem (Pierre Fabre Benelux N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Toctino (GSK, UK).

The choice of the reference product in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Study ZPS-602

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 30 healthy male subjects, aged 19-52 years. Each subject received a single dose (30 mg) of one of the two alitretinoin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours prior to the consumption of a standardized high-fat and high-calorie meal within 30 minutes prior to dosing. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 12, 14, 16, 20 and 24 hours after administration of the products.

The design of the study is acceptable. Normally, a single dose study under fasting conditions using the high strength is considered sufficient to support an application for immediate-release products with additional strengths. However, the current proposed products should be taken with a main meal. Hence, a study under fed conditions using the higher strength is appropriate and in line with the bioequivalence guideline. The meal is in accordance to the recommended high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. The sampling times are sufficient to provide a reliable estimate of the extent of exposure considering the T_{max} and half-life of alitretinoin. The washout period is considered appropriate to prevent carry-over effects.

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

Two subjects withdrew after period 1. Therefore 28 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 30 mg alitretinoin under fed conditions.

Treatment N=28	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	516.79 ± 149.46	524.18 ± 151.16	277.11 ± 96.15	2.75 (1.00 – 5.00)
Reference	516.13 ± 146.59	526.13 ± 146.59	260.77 ± 78.53	2.5 (1.00 – 4.50)
***Ratio (90% CI)**	1.00 (0.93 – 1.07)	0.99 (0.93 – 1.06)	1.04 (0.96 – 1.14)	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Study ZPS-650

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 31 healthy male subjects, aged 18-41 years. Each subject received a single dose (10 mg) of one of the two alitretinoin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours prior to the consumption of a standardized high-fat and high-calorie meal within 30 minutes prior to dosing. There were two dosing periods, separated by a washout period of seven days.

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, 8, 9, 10, 12, 14, 16, 20 and 24 hours after administration of the products.

The design of the study is acceptable. The procedures followed for a fed study are according to the bioequivalence guideline. The meal is in accordance to the recommended high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. The sampling time points are sufficient to provide a reliable estimate of the extent of exposure. The washout period is appropriate to prevent carry-over effects. However, four subjects had a washout period of 14 days as these subjects could not come as scheduled due to personal reasons. It is agreed that this did not impact the results. One subject had taken 500 mg paracetamol during the study conduct. This is considered not to have an impact on the analysis. The handling and processing of the plasma samples are according to standard procedures.

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
Thirty subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 10 mg alitretinoin under fed conditions.

Treatment N=30	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	150.05 ± 34.11	155.67 ± 33.74	86.26 ± 31.11	3.52 (1.00 – 9.00)
Reference	145.70 ± 33.46	153.47 ± 35.85	84.91 ± 31.68	2.40 (1.00 – 7.00)
***Ratio (90% CI)**	1.03 (0.98– 1.09)	1.02 (0.97 – 1.07)	1.01 (0.88 – 1.17)	--

$AUC_{0-\infty}$	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
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Alizem is considered bioequivalent with Toctino.

The MEB has been assured that the bioequivalence studies have 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).

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 Alizem.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Teratogenicity, foetal malformations • Benign intracranial hypertension (BIH) (pseudotumour cerebri) • Depression • Hyperlipidaemia and high CV risk patients • Anaemia

	• Photosensitivity • Xerophthalmia, dry eye syndrome • Inflammatory bowel disease (IBD) • Thyroid dysfunction
Important potential risks	• Extra-osseous calcifications • Bone demineralisation/osteoporosis • Diabetes mellitus (DM) • Use in patients with concurrent psychiatric disorders
Missing information	--

Routine risk minimisation is suggested for all of the safety concerns, except for the safety concern teratogenicity, for which an additional risk minimisation measure is proposed:

- A pregnancy prevention programme (PPP) according to the reference medicine.

The content of the educational materials as part of the PPP is laid down as outcome of the Art. 31 referral and will be implemented in agreement with and after assessment by the National Competent Authority.

IV.4 Discussion on the clinical aspects

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

V. USER CONSULTATION

The package leaflet (PL) 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 ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alizem 10 mg and 30 mg soft capsules has a proven chemical-pharmaceutical quality and is a generic form of Toctino 10 mg and 30 mg soft capsules. Toctino 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 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 Alizem 10 mg and 30 mg soft capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 December 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4058/001-002/IB/002	Change in the name of the medicinal product	--	8-3-2019	Approval	--
NL/H/4058/001/002/IA/001/G	Replacement of a manufacturer responsible for batch release	--	13-3-2019	Approval	--