Public Assessment Report

Scientific discussion

Acnenor
10 mg and 20 mg soft capsules
(Isotretinoin)

DK/H/2242/001-002/DC

7 May 2014

This module reflects the scientific discussion for the approval of Acnenor. The procedure was finalised on 3 September 2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Acnenor 10 mg and 20 mg soft capsules, from Actavis Group PTC ehf.

The product is indicated for*:* Severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.
A comprehensive description of the indications and posology is given in the SmPC.

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Roaccutan 10 mg and 20 mg soft capsules which has been registered in Denmark by Roche A/S, since 1985. For the purposes of data exclusivity, reference is made to the originator product Roaccutane 10 mg and 20 mg soft capsules which has been registered in the Community by Roche Products Limited UK, since 1983.

The reference products used for the bioequivalence studies are Roaccutane 20 mg capsules from the FR and NL market, respectively.

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

II. QUALITY ASPECTS

II.1 Introduction

Each soft capsule contains 10 mg or 20 mg isotretinoin, respectively.

The 10 mg capsules are light violet coloured, oval, soft gelatine capsules, containing a yellow/orange opaque viscous liquid, 10 mm x 7 mm in size.
The 20 mg capsules are maroon coloured, oval, soft gelatine capsules, containing a yellow/orange opaque viscous liquid, 13 mm x 8 mm in size.

The capsules are packed in PVC/PVDC-aluminum foil blisters in pack sizes of 10, 20, 30, 60 and 100 capsules. However, not all pack sizes may be marketed.

The excipients are: Soya-bean oil, refined; all-rac-alpha-tocopherol (E307); disodium edentate; butylhydroxyanisole (BHA E320); soya-bean oil (partly hydrogenated); hydrogenated vegetable oil and beeswax yellow.

The capsule shell contains: Gelatin; glycerol; sorbitol; purified water; titanium dioxide (E 171); cochineal red A (E124); black iron oxide (E172) (10 mg only) and indigotine lacquer (E132) (20 mg only).

The RMS 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.

II.2 Drug Substance

The drug substance isotretinoin is monographed in the Ph. Eur. It is a yellow or light orange crystalline powder. It is practically insoluble in water, soluble in methylene chloride and slightly soluble in 96% ethanol. It is sensitive to air, heat and light, especially in solution.

Isotretinoin is a conjugated compound of alternating single and double bonds; hence cis/trans structural isomers of isotretonoin exist (including tretinoin, which is listed and controlled under the Ph. Eur. Monograph). It is not optically active and does not display polymorphism.

The drug substance is sourced from two different external suppliers. Both active substance manufacturers have obtained EDQM certificates of suitability.

The control tests and specifications for drug substance applied by the finished product manufacturer are adequately drawn up.

Appropriate re-test periods have been set based on the CEP and on presented stability data, respectively.

II.3 Medicinal Product

The drug product is formulated as soft capsules, in two strengths, which are dose-proportional with respect to the capsule fill. The capsule fill contains the active substance in an oil-based suspension.
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients used are well known and of pharmacopoeial quality, except for the colouring agents, which are controlled according to relevant food legislation.

Relevant comparative dissolution profiles are provided, comparing the applied product and reference products marketed across Europe, including the test and reference products used in the two bioequivalence studies. The dissolution data demonstrate similar behavior to that of the reference products.

The manufacturing process has been adequately described and validated on commercial scale batches.

The product specifications cover appropriate parameters for this dosage form. The control tests and specifications for drug product are adequately drawn up. Validations of the analytical methods have been presented and are found adequate. Batch analysis has been performed on three recent commercial scale batches of each strength. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. A shelf-life of 3 years with no temperature storage restriction is supported by the presented stability data. The soft capsules are sensitive towards photo degradation and the blisters should be kept in the outer carton in order to protect from light.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of isotretinoin are well known. As Isotretinoin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers 77 publications up to year 2011. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Acnenor 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Isotretinoin is a well-known active substance with established efficacy and tolerability. As isotretinoin is a widely used, well-known active substance, the applicant has not provided additional studies (apart from bioequivalence studies referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical overview report refers 121 publications up to year 2011. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

Biowaiver

The MAH applies for waiver of the 10 mg strength. The following regulatory requirements are fulfilled:

a) The pharmaceutical products are manufactured by the same manufacturing process.
b) The qualitative composition of the different strengths is the same.
c) The compositions of the strengths are quantitatively proportional.
d) Appropriate in vitro dissolution data confirms the adequacy of waiving the 10 mg strength.

Bioequivalence studies

To support the application, the applicant has submitted two bioequivalence studies, comparing the 20 mg formulation strength of Acnenor to the same strength of the reference product, Roaccutane capsules by Roche.

The first study uses 2x20 mg capsules at the single dosing occasions of test and reference product. Since the pharmacokinetics of isotretinoin are linear over the therapeutic range (0.5-1.0 mg/kg) the dosage regime applied in the study could be considered acceptable in order to claim bioequivalence of the 20 mg test and 20 mg reference product. However, since the second study is considered more informative and more up to date, the first study will be considered as supportive only and only the newer study will be referenced below.

The study was an open-label, randomized, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fed conditions with a wash out period of 14 days between the two administrations. 20 mg was administered in each period.

The reference product used for the bioequivalence study is Roaccutane 20 mg capsules from the Dutch market.

Twenty four healthy male subjects participated in the study. 22 subjects completed the study and were included in the statistics.

Choice of primary variables and secondary PK variables:
The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, K_{el} and $t_{½\ el}$.
Primary variables: AUC_{0-t} and C_{max}.

90% confidence interval of the ratio (Test/Reference formulation) of the least square means from the ANOVA of the log-transformed $AUC_{0-\infty}$, AUC_{0-72h} and C_{max} of isotretinoin should be within the 0.8-1.25 acceptance range in order to conclude bioequivalence.

Results

(i) **Untransformed Data**

	$AUC_{0-\infty}$ (ng.hr/ml)	AUC_{0-72} (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)	$t_{½}$ (hr)
Isotretinoin 20 mg Capsule (Batch No.: 46611) (Test)					
Mean	5657.59	5391.80	429.37	4.27	16.56
S.D	1282.71	1262.52	94.17	1.56	2.96
Range	3817.46-7983.94	3590.09-7684.46	270.55-633.68	1.50-8.00	11.04-23.80
Roaccutane® 20 mg Capsule (Batch No.: B4538B71) (Reference)					
Mean	5253.56	4988.83	398.76	4.32	16.68
S.D	1124.75	1073.83	109.79	1.04	3.52
Range	3130.53-7679.99	2954.63-7225.38	250.35-735.16	2.50-6.00	12.63-25.49
P-Values	0.0403	0.0338	0.2003	0.8952	0.8242
Sequence	0.6650	0.7011	0.7639	0.5458	0.4736
Period	0.4558	0.3040	0.1744	0.0764	0.2461
Isotretinoin Capsule (Batch No.: 46611) (Test) vs Roaccutane® Capsule (Batch No.: B4538B71) (Reference)					
Mean Ratio % [a]	107.69	108.08	107.68	98.95	99.24
90% CI [b]	(1.016,1.137)	(1.020,1.142)	(0.977,1.177)	(0.853,1.126)	(0.934,1.051)

(ii) Log Data

	$AUC_{0-\infty}$ (ng.hr/ml)	AUC_{0-72} (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)
Isotretinoin 20 mg Capsule (Batch No.: 46611) (Test)				
Mean	3.7418	3.7202	2.6230	0.5975
S.D	0.1000	0.1031	0.0947	0.1855
Range	3.5818-3.9022	3.5551-3.8856	2.4322-2.8019	0.1761-0.9031
Roaccutane® 20 mg Capsule (Batch No.: B4538B71) (Reference)				
Mean	3.7105	3.6880	2.5869	0.6227
S.D	0.0971	0.0970	0.1093	0.1084
Range	3.4956-3.8854	3.4705-3.8589	2.3986-2.8664	0.3979-0.7782
Isotretinoin Capsule (Batch No.: 46611) (Test) vs Roaccutane® Capsule (Batch No.: B4538B71) (Reference)				
Mean Ratio % [a]	100.84	100.87	101.39	95.95

(iii) Geometric Data

	$AUC_{0-\infty}$ (ng.hr/ml)	AUC_{0-72} (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)
Isotretinoin 20 mg Capsule (Batch No.: 46611) (Test)				
Geometric Mean	5517.96	5250.17	419.72	3.96
S.D [c]	1271.06	1247.42	91.53	1.71
Range	3817.46-7983.94	3590.09-7684.46	270.55-633.68	1.50-8.00
Roaccutane® 20 mg Capsule (Batch No.: B4538B71) (Reference)				
Geometric Mean	5134.01	4874.93	386.31	4.19
S.D [c]	1150.32	1091.65	96.86	1.05
Range	3130.53-7679.99	2954.63-7225.38	250.35-735.16	2.50-6.00
P-Values	0.0353	0.0299	0.1508	-
Sequence	0.7430	0.7876	0.8518	-
Period	0.5234	0.3699	0.1606	-
Isotretinoin Capsule (Batch No.: 46611) (Test) vs Roaccutane® Capsule (Batch No.: B4538B71) (Reference)				
Mean Ratio % [a]	107.48	107.70	108.65	94.35
90% CI [b]	(1.017,1.136)*	(1.020,1.138)*	(0.987,1.196)*	-

The 90% confidence interval for the ratio between test and reference were within the acceptance criteria 80.00-125.00% for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} for the test product.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Aceneor 20 mg soft capsules can be considered bioequivalent with Roaccutane 20 mg soft capsules.
The results of the studies with the 20 mg formulation can be extrapolated to the other strength 10 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The RMS 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).

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 Acnenor.

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	Severe skin reactions
	Teratogenic effects
	Psychiatric Disorders- including depression, aggressive and/or violent behaviours
	Benign intracranial hypertension
	Severe increase in triglyceride levels, sometimes associated with acute pancreatitis
	Severe allergic reactions
Important potential risks	NA
Important missing information	NA

Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Severe skin reactions			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine pharmacovigilance	None proposed	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes current risk characterisation.

Teratogenic effects			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
Evaluate effectiveness of implementation of PPP.	Routine pharmacovigilance Special periodic safety reports (annual reports about PPP and integrated assessment of pregnancy exposures and outcomes) Pregnancy notification form	None proposed	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes current risk characterisation.

Psychiatric Disorders- including depression, aggressive and/or violent behaviours			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine pharmacovigilance	None proposed	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes current risk characterisation.

Benign intracranial hypertension			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine pharmacovigilance	None proposed	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes current risk characterisation.

Severe increase in triglyceride levels, sometimes associated with acute pancreatitis			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine pharmacovigilance	None proposed	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes current risk characterisation.

Severe allergic reactions			
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Proposed additional PhV activities	Objectives
None	Routine pharmacovigilance	None proposed	Ensure collection and assessment of all new data available in relation to this safety concern and evaluate how it changes current risk characterisation.

V. USER CONSULTATION

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 language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Acnenor 10 mg and 20 mg soft capsules has a proven chemical-pharmaceutical quality and is a generic form of Roaccutan. Roaccutan 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

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

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Acnenor with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 3 September 2013. Acnenor was authorised in Denmark on 7 October 2013.

According to the EURD list of 4 March 2014, PSURs for isotretinoin generics are required. PSUR submission frequency is 3 years with next DLP of 06-05-2015 and 04-08-2015.

The date for the first renewal will be: 3 September 2018.

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