COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Isotretinoïne GAP 5 mg, 10 mg and 20 mg, soft capsules

(isotretinoin)

NL/H/4820/001-003/DC

Date: 14 July 2020

This module reflects the scientific discussion for the approval of Isotretinoïne GAP. The procedure was finalised on 5 April 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
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 Isotretinoïne GAP 5 mg, 10 mg and 20 mg, soft capsules from GAP S.A.

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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Roaccutane 20 mg soft capsules, which has been registered by Roche Products (Ireland) Ltd since 19 April 1983.

The concerned member states (CMS) involved in this procedure were Denmark, Estonia, Ireland, Latvia, Lithuania, Norway and Sweden. The Irish reference product is used as a European Reference Product in the RMS and in CMSs Denmark and Sweden. For the remaining CMSs the medicinal product authorised in the Member State is selected.

The marketing authorisation has been granted pursuant to Article 10(1) (10 mg and 20 mg) and Article 10(3) (5 mg) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Isotretinoïne GAP 5 mg is a light orange, size 2, oval soft capsule.
Isotretinoïne GAP 10 mg is a violet, size 3, oval soft capsule.
Isotretinoïne GAP 20 mg is an off-white to cream, size 6, oval soft capsule.

The soft capsules are packed in blisters of orange PVC/TE/PVdC/aluminium foil.

The excipients are:
Capsule filling - all-rac-α-tocopheryl acetate, type II hydrogenated vegetable oil, hydrogenated soya-bean oil, beeswax yellow, refined soya-bean oil

Capsule shell - gelatine, glycerol, sorbitol liquid partially dehydrated, titanium dioxide (E-171), water purified

5 mg - iron oxide red (E-172), iron oxide yellow (E-172).

10 mg - patent blue V (E-131), ponceau red 4R (E-124).
20 mg - sunset yellow FCF (E-110).

The capsules of different strengths are dose/weight proportional.

II.2 Drug Substance

The active substance is isotretinoin, is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a yellow or light orange crystalline powder, which is soluble in chloroform, sparingly soluble in ether, slightly soluble in ethyl alcohol and isopropyl alcohol and practically insoluble in water. The active substance is not considered hygroscopic but very sensitive to oxygen and light exposure.

The CEP procedure is used for both manufacturers of 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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specifications adopted by the finished product manufacturer includes testing as per Ph. Eur. monograph for isotretinoin together with the additionally testing specified in the respective CEPs for residual solvents. The finished product manufacturer also controls the particle size of the drug substance and tests for palladium in line with CEP specification
Batch analysis data for four batches of the active substance from the first CEP holder and three batches of the active substance from the second CEP holder tested by the finished product manufacturer have been provided. Batch analysis results for all batches are within specification limits.

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

For the second manufacturer, results of stability testing have been provided. For the drug substance packed in the proposed container closure system, all results except for assay for some batches are within specification limits and no negative trends are observed following storage at long term conditions, intermediate conditions and at accelerated conditions up to 72 months or less. The stress stability study show that the related substances test of isotretinoin is stability indicating. Taking into consideration the stability batch data provided, the retest period of 24 months when packed under the proposed storage conditions has been granted.

II.3 Medicinal Product

Pharmaceutical development

The information on the development of the manufacturing process is considered sufficient.
The justification for the inclusion of the antioxidant all-rac-α-tocopheryl acetate is acceptable. The MAH also provided an extensive discussion on the excipients selection and concentration taking into consideration the solubility of the active substance, nature of the dosage form in this formulation and viscosity parameters. As the product is indicated for children 12 years and older, the MAH adequately discussed the suitability of the drug product in relation to the paediatric population as well as the use of azodyes at the current concentration.
The MAH provided comparative dissolution profiles of the generic test product Isotretinoïne GAP and the reference product Roaccutane. The studies have been performed using the BP method (QC method, 0.1M NaOH) for dissolution. Dissolution results for the BE batch show that the dissolution profiles between test and reference products can be considered similar. The specification limit for dissolution at release and shelf-life is set in line with the reflection paper (EMA/CHMP/CVMP/QWP/336031/2017).

Manufacturing process

The manufacturing process is a standard process involving manufacturing of the capsule fill material, production of gelatine mass, encapsulation, drying, sorting and packaging. The process has been well described.
Validation data for the 5 mg soft capsules were provided on three production scale batches. Blend uniformity has been demonstrated and all validation results were within acceptable limits. The process validation reports for the 10 mg and 20 mg capsules provided were more of a trend analysis report for batches manufactured between 2015 and 2017 rather than batches specific report. There were no out of specification result in the trend analysis data provided for isotretinoin 10 mg and 20 mg soft capsules. It can be concluded that the MAH can consistently produce a finished product that complies with all in-process and finished product specifications.

Control of excipients

All the excipients are known pharmaceutical ingredients that comply with the requirements of the Ph. Eur. except for partially hydrogenated soya bean oil that is described in the USP and colouring agents (iron oxide red, iron oxide yellow, patent blue V, ponceau red 4R and

sunset yellow FCF) that are described in the USP and Ph. Fr. 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 appearance, uniformity of fill mass, disintegration, content uniformity, dissolution, identification, assay, chromatographic purity, loss on drying, identification of the antioxidant, antioxidant assay, identification of colourants and microbiological quality. The finished product specifications for release and shelf-life of the drug product are adequately drawn up. Identification tests were also included in the shelf-life specification. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on four production-scale batches for each strength. The results demonstrate compliance with the proposed release specifications.

Stability of drug product

Stability studies have been performed on three production-scale batches of the drug product for each strength. The stability studies have been performed in line with stability guidelines. The testing frequency and storage conditions are also in line with the said guidelines. A photostability study was performed on one batch of each strength of the drug product in line with ICH guideline ICH Q1B.

All results are within specification limits and no specific trends were observed, following three batches of each strength stored at accelerated, intermediate and long-term conditions. Additionally, the MAH has placed one batch from each strength manufactured using the other active substance supplier in stability studies.

The MAH has provided 36-month real time stability data to justify the claimed shelf-life of 36 months.

In line with ICH Q1B, photostability testing showed that the product is photosensitive. As no significant changes are observed at accelerated conditions, the storage restriction is 'This medicinal product does not require any special temperature storage conditions. Store in the original package and keep blister in the outer carton in order to protect from light.'

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

Excipients which may potentially originate from an animal source are gelatine and glycerol. The supplier for glycerol has submitted TSE/BSE risk declaration stating that this excipient is obtained from vegetable origin crude glycerines. The MAH submitted CEPs issued by the EDQM for gelatine used in the manufacturing of the soft capsules.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Isotretinoïne GAP 5 mg, 10 mg and 20 mg, soft capsules 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 Isotretinoïne GAP 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 Roaccutane, 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

Isotretinoin 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product for Isotretinoïne GAP 40 mg (GAP S.A., Greece) is compared with the pharmacokinetic profile of the reference product Roaccutane 20 mg soft capsule (Roche Products Limited, United Kingdom).

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

Biowaiver

The MAH applied for 20, 10 and 5 mg strengths, based on a bioequivalence study with 40 mg capsules. All conditions for biowaiver are met

- All 4 strengths are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components. Capsule shell, colour agents and flavours are not required to follow this rule)
- Appropriate in-vitro dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing. Dissolution testing has been performed at recommended three physiological pH levels of 1.2, 4.5 and 6.8.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 46 healthy male subjects, aged 18-54 years. Subjects received either 1 soft capsule (=40 mg isotretinoin) of the test formulation or 2 soft capsules (=40 mg isotretinoin) of the reference product, 30 minutes after the start of the standard high-fat breakfast. The high-fat breakfast (total calorific value of 1004.32 kcal) had the following composition: 2 eggs fried in 10 g butter, 2 strips of bacon, 2 slices of toast with 10 g butter, 120 g hashed brown potatoes with 10 g butter and 240 mL whole milk. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected -10:00, -2:00, pre-dose (0:00) and 0:30, 1:00, 2:00, 3:00, 3:30, 4:00, 4:30, 5:00, 5:30, 6:00, 7:00, 8:00, 9:00, 10:00, 12:00, 24:00, 36:00, 48:00 and 72:00 hours after administration of the products.

The design of the study is acceptable. As isotretinoin should be taken with food, a study under fed conditions is required. The composition of the breakfast can be classified as high fat and high caloric and is acceptable. The mean half-life of isotretinoin is about 19 hours and of one of the metabolites (4-oxo-isotretinoin) 29 hours. Therefore plasma sampling until 72 hours after dosing and a wash-out period of 14 days is considered sufficient.

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 during the first stage at own request and was replaced by another subject. Forty-six subjects were eligible for pharmacokinetic analysis.

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

Treatment N=46	AUC_{0-72} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	8810.22 ± 2216.76	697.36 ± 223.10	4.5 (1.0-10.0)	--
Reference	8581.25 ± 2310.00	638.86 ± 242.11	4.5 (1.0-9.0)	--
***Ratio (90% CI)**	1.04 (0.96-1.12)	1.11 (1.02-1.22)	--	--
CV (%)	18.97	22.37	--	--

$AUC_{0-\infty}$	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 study
The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Isotretinoïne GAP 40 mg is considered bioequivalent with Roaccutane 20 mg soft capsules.

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).

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 Isotretinoïne GAP.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Teratogenicity and congenital malformations • Eye disorders • Musculoskeletal and connective tissue disorders

	• Severe cutaneous adverse reactions
Important potential risks	• Psychiatric disorders • Inflammatory bowel disease (ulcerative colitis and Chron's disease)
Missing information	• None

The member states agreed that routine pharmacovigilance activities are sufficient for the risks and areas of missing information. The MAH will provide educational material, which should contain the following key elements:

Pregnancy Prevention Program
- o Patient reminder card
- o Physician's checklist/Acknowledge form for prescribing to female patients
- o Pharmacist checklist

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Roaccutane soft capsules. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg soft capsules (UK/H/3577/001-004/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet. The member states agree that the presented package leaflet reflects the current safety messages of this product and is written in line with current guidance and therefore fulfils the requirements for bridging.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Isotretinoïne GAP 5 mg, 10 mg and 20 mg soft capsules have a proven chemical-pharmaceutical quality and are hybrid/generic forms of Roaccutane soft capsules. Roaccutane 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 Isotretinoïne GAP with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 April 2020.

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