CBG MEB

Public Assessment Report

Scientific discussion

Isotretinoïne SUN 10 mg and 20 mg, soft capsules

(isotretinoin)

NL/H/3739/001-002/DC

Date: 8 February 2018

This module reflects the scientific discussion for the approval of Isotretinoïne SUN 10 mg and 20 mg, soft capsules. The procedure was finalised on 12 April 2017. 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
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
EDMF	European Drug Master File
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 SUN 10 mg and 20 mg, soft capsules from Sun Pharmaceutical Industries Europe B.V.

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 anti-bacterials 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 10 mg and 20 mg soft capsules which has been registered in the United Kingdom by Roche Products Limited since 30 June 1983. In the Netherlands, the reference product Roaccutane 10 mg and 20 mg soft capsules was registered by Roche Nederland B.V. on 25 April 1984.

The concerned member states (CMS) involved in this procedure were Germany, Spain, Hungary, Italy, Poland, Romania and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Isotretinoin SUN is oval shaped, light pink coloured (10 mg) or orange to reddish orange coloured (20mg), opaque soft capsule, imprinted with 'RR' containing a orange-yellow coloured oily suspension. Each soft capsule contains 10 mg or 20 mg of isotretinoin.

The soft capsules are packed in PVC/PE/PVDC/aluminium/polyester/paper blisters.

The excipients are:
Capsule filling – hydrogenated soya-bean oil, beeswax white, disodium edetate, butylhydroxyanisole (E320), soyabean oil refined and polysorbate 80
Capsule shell – gelatin, glycerol (E422), red iron oxide (E172), titanium dioxide (E171) and light liquid paraffin
Printing ink – shellac glaze (45%, 20% esterified, in ethanol), black iron oxide (E172) and propylene glycol (E1520).

II.2 Drug Substance

The active substance is isotretinoin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Isotretinoin is a yellow or light-orange, crystalline powder and practically insoluble in water, soluble in methylene chloride and slightly soluble in ethanol (96%). Only one crystalline polymorphic form is known for isotretinoin, which is consistently produced by the manufacturer.

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 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 monograph in the Ph.Eur. with additional tests and limits for residual solvents, butylhydroxyanisole and particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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. The objective of the development was to produce a product a generic product of the originator product Roaccutane soft capsules. The qualitative composition of the reference product and further design and functionality aspects of the capsule was taken as the basis for formulation development and optimisation, including the capsule fill weight and shape, and dissolution.
A bioequivalence study has been performed between test product Isotretinoin SUN 20 mg and reference product Roaccutane 20 mg. For the 10 mg strength, a biowaiver has been requested. Attempts were made to compare dissolution profiles for the biowaiver, at pH 1.2, 4.5 & 6.8, between the two product strengths of the proposed product and also to compare dissolution with the reference product in the same strengths. However, no profiles could be generated at the 3 pH's; in all cases 0% was dissolved at time points T5min - T60min, due to the poor solubility of the drug substance. Thus these conditions dissolution similarity has been demonstrated (in all cases zero) and the dissolution is considered acceptable.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The process is a non-standard process as the drug substance is suspended in the capsule. The main steps are: processing of the gelatine mass preparation (capsule wall), processing of the mixture of the drug substance and the oily basis (capsule fill), encapsulation step and drying of the filled capsules. Process validation data on the product have been presented for 3 production batches in accordance with the relevant European guidelines.

Control of excipients
The excipients, with exception of the colourants, comply with the Ph. Eur. or United States National Formulary. The colourants comply with he EU directive. 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, identity, assay, related substances/degradation products, disintegration, dissolution, microbial purity, content of butylhydroxyanisole, uniformity of dosage units and average fill weight. The release and shelf-life requirements/limits are identical with the exception of the limits for related substances; the shelf-life limits for these parameters are slightly wider. This is acceptable. 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 on three production batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product were included for three production scaled bathes per strength stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. The results were within the proposed specification limits. The photostability study shows

that the product is not light resistant. Therefore, the statement: 'Store in the original package. Keep the blister in the outer carton in order to protect from light.' is included. On basis of the data submitted, the proposed shelf-life of two years, no special temperature storage conditions, in the proposed blister is considered justified.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no TSE risk substances of animal origin present in the product. For gelatine, the excipient of animal origin, a valid EDQM TSE CEP has been submitted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Isotretinoïne SUN 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 SUN 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Isotretinoïne SUN 20 mg, soft capsules (Sun Pharmaceutical Industries Europe B.V., NL) is compared with the pharmacokinetic profile of the reference product Roaccutane 20 mg soft capsules (Roche Products Limited, UK).

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

Biowaiver
The following prerequisites for requesting a biowaiver for the 10 mg strength based on the bioequivalence study with the highest strength of 20 mg are met:

- the strengths have been manufactured by the same manufacturing process
- the compositions are qualitatively similar and quantitatively dose proportional
- plasma pharmacokinetics of isotretinoin can be considered dose linear in the dose range of 10-20 mg, based on the SmPC of the originator.

At the usual pH conditions of 1.2, 4.5 and 6.8 the dissolution at all time points was zero. Therefore, at these conditions dissolution similarity between both strengths has been demonstrated and a biowaiver for the lower strength of 10 mg can be granted.

Bioequivalence studies

Design

A two-stage, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions. 44 healthy male subjects, aged 20-44 year were enrolled in the first stage as per study protocol. Since bioequivalence was reached after the first stage, the second stage was not required to be performed and no further patients were enrolled.
required to be performed and no further patients were enrolled. Each subject received a single dose (20 mg) of one of the 2 isotretinoin formulations. The tablet was orally administered with 240 ml water after a high fat high calorie breakfast (consisting of white bread, butter, paneer, onion, tomato, oil, salted peanut, whole milk and sugar) There were 2 dosing periods, separated by a washout period of 25 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 10.0, 11.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0, 30.0, 36.0, 48.0 and 72.0 after administration of the products.

The design (including the blood sampling scheme) is acceptable. As isotretinoin should be taken with food, a study under fed conditions is required. 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 25 days should be sufficient.

Analytical/statistical methods

Initially, the statistical analysis did not take into account the multiple testing that is performed in a 2 stage design study. For such a design, the analysis of the first stage data should be treated as an interim analysis and both analyses (first and second stage) should be conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%). The MAH was asked to re-analyse the data using a 94.12% CI. These data have been provided (see below).

Results

One subject was withdrawn from the study due to an adverse event (vomiting) in the first period of the study. In the second period of the study, 6 subject dropped out due to personal situation, changes at work or at home. After the second period, one subject had emesis and was excluded from analysis. Therefore, 36 subjects completed the study and 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=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4757 ± 1389	5159 ± 1501	370 ± 116	4.5 (1.0 – 10.0)	18.1 ± 4.0
Reference	4918 ± 1152	5330 ± 1292	396 ± 125	5.0 (1.0 – 10.0)	18.4 ± 4.3
***Ratio (94.12% CI)**	0.95 (0.84 – 1.05)	0.95 (0.86 – 1.04)	0.94 (0.87 – 1.04)	--	--

$AUC_{0-\infty}$ 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*

Conclusion on bioequivalence studies:
The 94.12% 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 study is considered bioequivalent with Reference medicinal product.

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 SUN.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Teratogenicity • Psychiatric disorders including depression, suicidality and anxiety • Severe skin reactions including SJS and TEN • Eyes disorders including corneal opacities, reduced night vision and keratitis • Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis
Important potential risks	• Gastrointestinal disorders including inflammatory bowel disease
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Roaccutane. 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

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 with 9 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Isotretinoïne SUN 10 mg and 20 mg, soft capsules have a proven chemical-pharmaceutical quality and are generic forms of Roaccutane 10 mg and 20 mg 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 SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 April 2017.

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/3739/1-2/IA/001	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006; Implementation of wording agreed by the competent authority	Yes	20-12-2017	Approved	-