Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

UKPAR

Isotretinoin 10mg Capsules, soft

(isotretinoin)

UK Licence Number: PL 40739/0041

Ennogen Healthcare Limited

LAY SUMMARY

Isotretinoin 10mg Capsules, soft
(isotretinoin)

This is a summary of the Public Assessment Report (PAR) for Isotretinoin 10mg Capsules, soft (PL 40739/0041). It explains how Isotretinoin 10mg Capsules, soft were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Isotretinoin 10mg Capsules, soft.

The product will be referred to as 'Isotretinoin Capsules' throughout the remainder of this lay summary.

For practical information about using Isotretinoin Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Isotretinoin Capsules and what are they used for?
Isotretinoin Capsules are a 'generic medicine'. This means that Isotretinoin Capsules are similar to a 'reference medicine' already authorised in the European Union (EU) called Roaccutane 10mg soft gel Capsules authorised to (Roche Products Limited).

Isotretinoin soft capsules contain the active ingredient isotretinoin. Isotretinoin is used to treat severe forms of acne (such as nodular or conglobate acne, or acne at risk of permanent scarring) which has not got better after other anti-acne treatments, including oral antibiotics.

How do Isotretinoin Capsules work?
This medicine contains the active substance called isotretinoin. This is a vitamin A derivative, belonging to the retinoid class of medicines. Isotretinoin is active against all four causes of acne — excess oil production, clogged pores in the skin, too much of the bacteria *P. acnes*, and inflammation.

How are Isotretinoin Capsules used?
The pharmaceutical form of this medicine is a soft gel capsule and the route of administration is oral (by mouth). The capsule should be swallowed whole with a drink of water.

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

- The capsules should be taken with food once or twice daily.
- The capsules should be swallowed whole, and not chewed or sucked.

Occasionally acne may get worse during the first weeks of treatment, but with continued treatment should improve.

Dose
The patient's doctor will prescribe an individual dose in accordance with their patient's body weight and other clinical parameters like renal insufficiency, etc.

The specific individual doses might be better matched by other available product strengths.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Isotretinoin Capsules are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription. Isotretinoin should only be prescribed by or under the supervision of a dermatologist (a doctor specialised in the treatment of skin problems) with understanding of the risks of isotretinoin therapy and monitoring requirements.

What benefits of Isotretinoin Capsules have been shown in studies?
Because Isotretinoin Capsules are a generic medicine, studies in patients have been limited to tests to determine that Isotretinoin Capsules are considered to be bioequivalent to the reference medicine Roaccutane 10mg soft gel Capsules authorised to (Roche Products Limited).

Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Isotretinoin Capsules?
Because Isotretinoin Capsules are a generic medicine and they are considered to be bioequivalent to the reference medicine Roaccutane 10mg soft gel Capsules authorised to (Roche Products Limited), their benefits and possible side effect are taken as being the same as those of the reference medicine.

For a full list of all the side effects reported with Isotretinoin Capsules see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

Why are Isotretinoin Capsules approved?
It was concluded that, in accordance with EU requirements, Isotretinoin Capsules have been shown to have comparable quality and are considered to be bioequivalent Roaccutane 10mg soft gel Capsules authorised to (Roche Products Limited). Their benefits are greater than the risks and it was recommended that Isotretinoin Capsules can be approved for use.

What measures are being taken to ensure the safe and effective use of Isotretinoin Capsules?
A risk management plan (RMP) has been developed to ensure that Isotretinoin Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Isotretinoin Capsules including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/ reviewed continuously.

Other information about Isotretinoin Capsules
A marketing authorisation was granted in the UK on 20 September 2018.

The full PAR for Isotretinoin Capsules follows this summary.

For more information about treatment with Isotretinoin Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Ennogen Healthcare Limited, a marketing authorisation for the medicinal product Isotretinoin 10mg Capsules, soft (PL 40739/0041). This product is a prescription-only medicine (POM) 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.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference product for this application is Roaccutane 10mg soft gel Capsules authorised in the UK on 30 June 1983 to the marketing authorisation holder (MAH) Roche Products Limited (PL 00109/0133).

Isotretinoin, a synthetic vitamin A derivative, is a retinoid that is effective against severe acne. Its exact mechanism of action 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.

Pregnancy is an absolute contraindication to treatment with isotretinoin (see section 4.3 of the summary of product characteristics available on the MRHA website). Women of childbearing potential must use effective contraception during and up to one month after treatment. If pregnancy does occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe and serious malformation of the fetus.

No new clinical or non-clinical studies were submitted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. A bioequivalence study was not required as the basis for a biowaiver was adequately justified.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II QUALITY ASPECTS

II.1 Introduction

The finished product is a soft gelatin capsule containing 10mg isotretinoin per capsule. Other ingredients consist of the pharmaceutical excipients refined soya-bean oil, All-rac-α-tocopherol, disodium edetate, butylhydroxyanisole, partly hydrogenated soya bean oil, yellow beeswax, and hydrogenated vegetable oil. The Capsule filling consists of gelatin, glycerol, non-crystallising sorbitol solution 70% (E420), Erythrosine colourant soluble (E127), Titanium dioxide (E171), purified water, and Black iron oxide (E172).

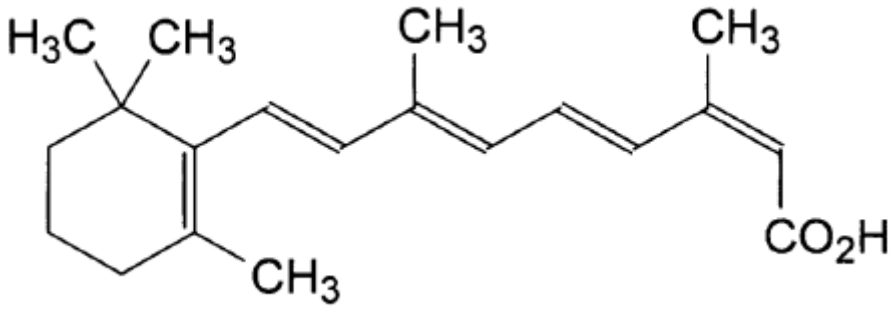
The product is packaged in polyvinyl chloride (PVC) / polyvinylidene chloride (PVdC) / Aluminium (Alu) blister packs containing 28, 30, 56, and 60 capsules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN:	Isotretinoin
Chemical name:	(13Z)-15-Apo-β-caroten-15-oic acid; (2Z,4E,6E,8E)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid.

Structure:



Molecular formula:	$C_{20}H_{28}O_2$
Molecular mass:	300.4
Appearance:	A yellow or light orange crystalline powder.
Solubility:	Practically insoluble in water, soluble in methylene chloride, and slightly soluble in 96 % ethanol.

All aspects of the manufacture and control of the active substance, isotretinoin, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a safe, efficacious, soft capsule containing 10mg isotretinoin, that is a generic version of the reference product Roaccutane 10mg soft gel Capsules authorised to (Roche Products Limited). The development of the product has been described, the choice of excipients is justified and their functions explained.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

The excipients, included in the capsule fill are controlled by Ph Eur monographs, with the exceptions of hydrogenated vegetable oil and partly hydrogenated soya-bean oil. Hydrogenated vegetable oil complies with the British Pharmacopoeia (BP), while partly hydrogenated soya-bean oil complies with the German Pharmacopoeia (DAB) except that the melting point test (Ph. Eur. 2.2.15) may be replaced by the drop point test (Ph. Eur. 2.2.17).

The excipients included in the capsule shell are controlled by Ph Eur, with the exceptions of iron oxide, black (E172) and Erythrosine colourant soluble (E127). Iron oxide, black and Erythrosine colourant soluble (E127) are stated to be controlled by European Parliament and Council Directive No. 2008/128/EC on Specific Purity Criteria Concerning Colours for Use in Foodstuffs. Declarations are provided from suppliers of these colorants stating compliance with Regulation (EU) No. 231/2012, applying from December 01, 2012 laying down specifications for food additives listed in Annexes II and III to Regulation 1333/2008/EC.

Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on commercial batch sizes have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with the storage conditions of “Do not store above 30°C. Store in the original container. Keep container in the outer carton. Keep out of the sight and reach of children”.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of isotretinoin are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Isotretinoin 10mg Capsules, soft are intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of isotretinoin are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of isotretinoin.

IV.2 Pharmacokinetics

No bioequivalence (BE) studies comparing the Isotretinoin 10mg soft gel Capsules with the equivalent strength of the originator have been submitted. Instead the Applicant submitted the findings of a BE study with a higher strength of product, Isotretinoin 20mg capsules and requested a biowaiver which was accepted as the requirements of CPMP/EWP/QWP/1401/98 Rev. 1 were met.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new data on safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL), which is acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the competent authority;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

V User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to called Isotretinoin 5mg capsules (Ennogen Healthcare Limited). The bridging report submitted by the applicant has been found acceptable.

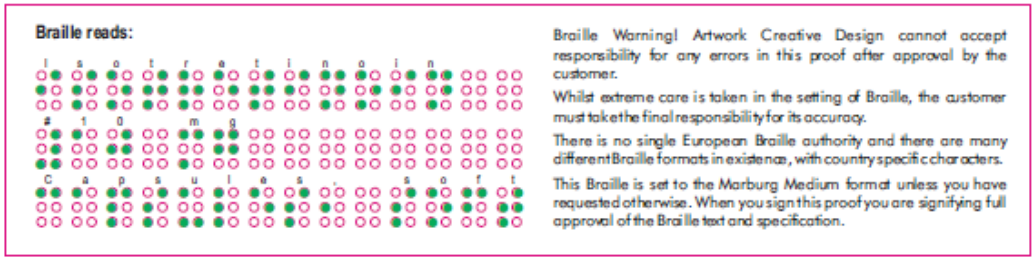
VI Overall conclusion, benefit/risk assessment and recommendation

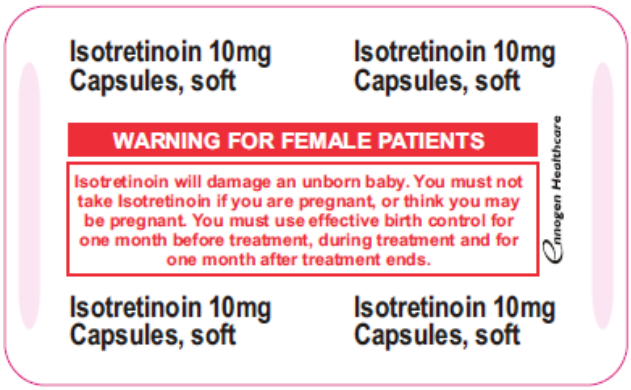
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with isotretinoin is considered to have demonstrated the therapeutic value of the compound. The results of the clinical study confirm that the product is bioequivalent to the reference product and its benefit-risk is, therefore, considered to be positive.

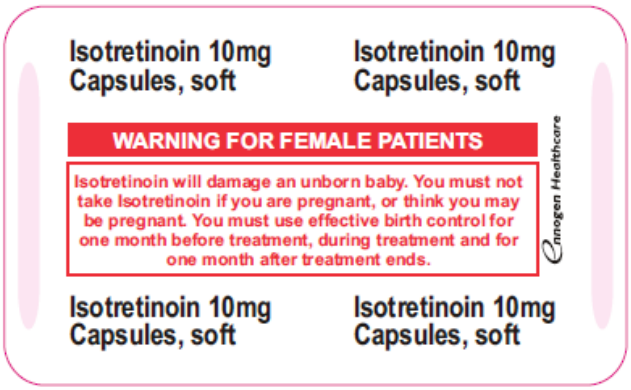
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The MAH has submitted the following approved labelling for this medicine which is presented below:




Isotretinoin 10mg Capsules, soft
Isotretinoin 10mg Capsules, soft
WARNING FOR FEMALE PATIENTS
Isotretinoin will damage an unborn baby. You must not take Isotretinoin if you are pregnant, or think you may be pregnant. You must use effective birth control for one month before treatment, during treatment and for one month after treatment ends.
Ennogen Healthcare
Isotretinoin 10mg Capsules, soft
Isotretinoin 10mg Capsules, soft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Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)