Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

DESOGESTREL 75 MICROGRAMS FILM-COATED TABLETS

(desogestrel)

Procedure No: UK/H/5253/001/DC

UK Licence No: PL 30306/0437

Actavis Group PTC ehf.

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Desogestrel 75 micrograms Film-coated Tablets (PL 20011/0006; UK/H/5253/001/DC). It explains how the application for Desogestrel 75 micrograms Film-coated Tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Desogestrel 75 micrograms Film-coated Tablets, patients should read the Package Leaflet or contact their doctor or pharmacist.

What are Desogestrel 75 micrograms Film-coated Tablets and what are they used for?
Desogestrel 75 micrograms Film-coated Tablets are a 'generic medicine'. This means that Desogestrel 75 micrograms Film-coated Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Cerazette 75 microgram film-coated tablets.

Desogestrel is a hormone contraceptive, used to prevent pregnancy.

How do Desogestrel 75 micrograms Film-coated Tablets work
Desogestrel is a progesterone-only pill (POP or mini-pill). Most POPs or mini-pills work by preventing the sperm cells from entering the womb, but they do not always prevent the egg cell from ripening. Desogestrel is different from other mini-pills in that it has a dose that in most cases will prevent the egg cell from ripening. As a result, Desogestrel is a highly effective contraceptive.

In contrast to the combined pill (which contain an oestrogen hormone in combination with a progestogen), Desogestrel can be used by women who do not tolerate oestrogens and by women who are breast feeding. A disadvantage is that vaginal bleeding may occur at irregular intervals during the use of Desogestrel. On the other hand, there may not be any bleeding at all.

How are Desogestrel 75 micrograms Film-coated Tablets used?
The pack contains 28 tablets. The days of the week are printed on the blister and arrows are printed indicating the order to take the pills. Each day corresponds with one tablet.

Every time a new pack of Desogestrel is started, a tablet should be taken from the top row. One tablet a day should be taken until the pack is empty, following the direction indicated by the arrows.

Tablets should be taken at about the same time each day and should be swallowed whole with water. Some bleeding may occur during the use of Desogestrel, but use should be continued as normal. When a pack is empty, a new pack should be started on the next day, without interruption and without waiting for a bleed.

This medicine can only be obtained with a prescription.

What benefits of Desogestrel 75 micrograms Film-coated Tablets have been shown in studies?
Because Desogestrel 75 micrograms Film-coated Tablets are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Cerazette 75 microgram film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Desogestrel 75 micrograms Film-coated Tablets?
Because Desogestrel 75 micrograms Film-coated Tablets are a generic medicine, their possible side effects are taken as being the same as those of the reference medicine, Cerazette 75 microgram film-coated tablets.

For the full list of all side effects reported with Desogestrel 75 micrograms Film-coated Tablets, see section 4 of the package leaflet.

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

Why are Desogestrel 75 micrograms Film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, Desogestrel 75 micrograms Film-coated Tablets have been shown to have comparable quality and to be bioequivalent to Cerazette 75 microgram film-coated tablets. Therefore, the MHRA decided that, as for Cerazette 75 microgram film-coated tablets, the benefits outweigh the identified risks and recommended that Desogestrel 75 micrograms Film-coated Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Desogestrel 75 micrograms Film-coated Tablets?
Safety information has been included in the Summary of Product Characteristics, and the package leaflet for Desogestrel 75 micrograms Film-coated Tablets, 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 and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Moviprep Orange Powder for Oral Solution
On 09 June 2013, Belgium, Denmark, Estonia, Ireland, Lithuania, Luxembourg, Latvia, Poland, Romania, Slovakia and the UK agreed to grant a Marketing Authorisation for Desogestrel 75 micrograms Film-coated Tablets. After the national phase, a Marketing Authorisation was granted in the UK on 02 July 2013.

The Marketing Authorisation was subsequently cancelled in Luxembourg on 27 March 2015.

The full PAR for Desogestrel 75 micrograms Film-coated Tablets follows this summary.

For more information about treatment with Desogestrel 75 micrograms Film-coated Tablets, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in November 2015.

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Desogestrel 75 micrograms Film-coated Tablets (PL 30306/0437; UK/H/5253/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Belgium, Denmark, Estonia, Ireland, Lithuania, Luxembourg, Latvia, Poland, Romania and Slovakia as Concerned Member States (CMS).

This product is a prescription-only medicine (legal classification POM).

This was an application made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Cerazette 75 mikrog Filmdragered tablet (NV Organon, Sweden), which was initially granted a marketing authorisation in the EU on 12 December 1997. The UK reference product is Cerazette 75 microgram film-coated tablets (Organon Laboratories, PL 00065/0159). The reference product used in the bioequivalence study was Cerazette 75 microgram film-coated tablets (Organon Espanola, S.A.).

Desogestrel is indicated for use as an oral contraceptive. It is a progestogen-only pill, which contains the progestogen desogestrel. In contrast to traditional progestogen-only pills, the contraceptive effect of Desogestrel is achieved primarily by inhibition of ovulation. Other effects include increased viscosity of the cervical mucus. It is suitable for use whilst breastfeeding and for women who cannot or do not wish to use oestrogens.

No non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

A bioequivalence study was performed, which compared the pharmacokinetics of the test product Desogestrel 75 micrograms Film-coated Tablets (Actavis Group) to those of the Spanish reference product Cerazette 75 microgram film-coated tablets (Organon Espanola, S.A.). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved at the end of procedure on 09 June 2013. After a subsequent national phase, a licence was granted in the UK on 02 July 2013.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 75 micrograms of desogestrel. Other ingredients consist of the pharmaceutical excipients, as follows:

Tablet core: lactose monohydrate, maize starch, povidone K30 (E1201), d-α-tocopherol (E307), soybean oil, colloidal hydrated silica (E551), colloidal anhydrous silica, (E551) and stearic acid (E570)

Coating: hypromellose 2910 (E464), polyethylene glycol and titanium dioxide (E 171)

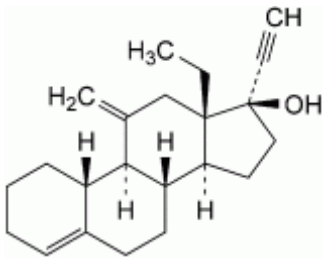
The finished product is packaged in polyvinylchloride/polyvinylidene chloride film and aluminium push through foil blisters, containing 28 tablets per blister. Blisters are packaged in a cardboard carton in pack sizes of 1 x 28 tablets, 3 x 28 tablets or 6 x 28 tablets.

The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

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

rINN: Desogestrel
Chemical name: 13-Ethyl-11-methylidene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol
Structure:



Molecular formula: $C_{22}H_{30}O$
Molecular weight: 310.5
Solubility: Practically insoluble in water, slightly soluble in ethanol and in ethyl acetate and sparingly soluble in hexane.

With the exception of the packaging and stability data, which were submitted separately, all aspects of the manufacture and control of desogestrel are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the currently licensed product, Cerazette 75 microgram film-coated tablets (Organon Laboratories Limited, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed product and its respective reference product.

The excipients contained within the coating comply with suitable in-house standards and the d-α-tocopherol (E307) complies with its United States Pharmacopeia monograph. All other excipients comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients are sourced from animal or human origin. The milk used in the production of the lactose monohydrate is sourced from healthy animals under the same conditions as milk intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three commercial-scale batches of finished product. The results are satisfactory.

Finished Product Specification

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

Stability of the product

Stability studies were performed, in accordance with current guidelines, on pilot-scale batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years, with no special storage conditions. The applicant has committed to placing the first three commercial scale batches and thereafter at least one batch annually, under long-term stability testing conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects

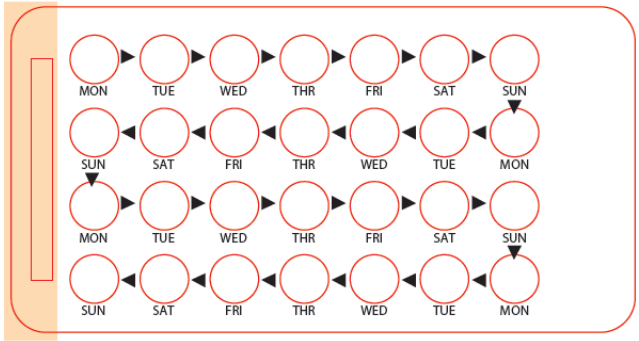
It is recommended that a Marketing Authorisation is granted for Desogestrel 75 micrograms Film-coated Tablets.

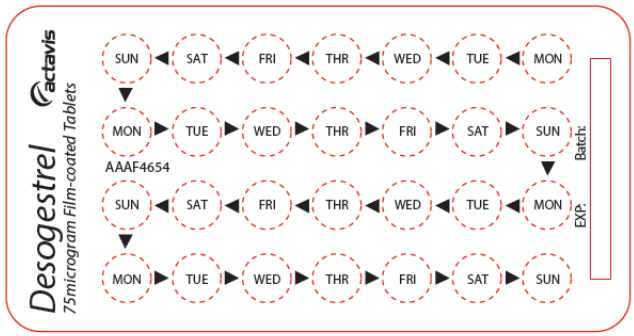
II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

The currently approved labels are presented below:





III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of desogestrel are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology

No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

The applicant has provided an in depth ERA primarily based upon data from the literature. This is satisfactory.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Desogestrel 75 micrograms Film-coated Tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction

With the exception of the bioequivalence study detailed below, no new clinical studies have been performed and none are required for this type of application. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

In support of this application, the applicant submitted the following bioequivalence study:

A randomised, open-label, two-way crossover, bioequivalence study comparing the pharmacokinetics of the test product Desogestrel 75 micrograms Film-coated Tablets (Actavis Group) versus the reference product Cerazette 75 microgram film-coated tablets (Organon Espanola, S.A.) in healthy subjects under fasting conditions.

Volunteers were given each treatment after an overnight fast of 12 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. Each regimen was separated by a 28-day washout period.

Treatments were as follows:
Test: A single dose (one tablet) of Desogestrel 75 micrograms Film-coated Tablets (manufactured by Laboratorios León Farma, S.A., Spain), given orally with 200 ml of water

Reference: A single dose (one tablet) of Cerazette 75 microgram film-coated tablets (manufactured by Organon Espanola, S.A laboratories), given orally with 200 ml of water

A summary of the pharmacokinetic results is presented in the tables below:

PK Parameter	Leon Farma Test			Cerazette Reference		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-72} (pg.h/mL)	5352.33	1853.50	34.63	5126.45	1580.18	30.82
C_{max} (pg/mL)	843.28	305.24	36.20	823.88	264.14	32.06
T_{max} (h)	1.39	0.61	44.07	1.54	0.71	46.15
T_{max} (h) (median and interquartile ranges)	1.25	0.50	-	1.25	0.25	-
SD = standard deviation; CV: coefficient of variation						

	Ratio LSM T/R (%)	90% geometric CI (%)	ISCV (%)
AUC_{0-72}	104.18	98.59-110.09	14.87
C_{max}	100.54	92.09-109.76	23.85
T: Leon Farma Test; R: Cerazette Reference LSM: least squares mean; CI: confidence interval; ISCV: intra-subject coefficient of variation			

Compared with the reference product, the 90 % confidence intervals for the test product are within 80.00-125.00 % for C_{max} and AUC. Desogestrel 75 micrograms Film-coated Tablets are, therefore, considered bioequivalent with Cerazette 75 microgram film-coated tablets.

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for an application of this type.

IV.5 Clinical Safety

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

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

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Desogestrel 75 micrograms Film-coated Tablets.

V. USER CONSULTATION

The results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for Desogestrel 75 micrograms Film-coated Tablets was provided. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with desogestrel is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

Table of content of the PAR update for MRP and DCP

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)
To submit a revised Environmental Risk Assessment.	UK/H/5253/ 001/1B/004	No	20/08/2015	30/10/2015	Approval	Yes

Annex I

Reference: PL 30306/0437 - 0008
Product: Desogestrel 75 micrograms Film-coated Tablets
Marketing Authorisation Holder: Actavis Group PTC ehf.
Active Ingredients: Desogestrel
Reason: To submit a revised Environmental Risk Assessment.

Background

As part of the original assessment the applicant provided an in depth Environmental Risk Assessment (ERA) primarily based upon data from the literature. The applicant indicated that additional studies designed to detect the effects of endocrine disruptors in accordance with the CHMP *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/HMP/SWP/4447/00) would be performed. However, the applicant subsequently suggested that there are sufficient data in the literature; hence, a revised ERA based on data from the literature only, has been submitted.

Supporting Evidence

A revised ERA has been provided.

Assessor's Comment

Given that this is a generic product and there is unlikely to be an increase in environmental exposure and there is extensive literature data on the environmental impact of this class of compound, the value of generating in vivo fish toxicology data is questioned. These will not provide any more helpful impactful data (than that already in the literature) for the assessment of environmental risk. The original assessment provided by the applicant is considered adequate, thus this variation is approved.

Conclusion

The grant of this variation is recommended.

Decision - Granted
Date - 30 October 2015