COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Desogestrel Centrafarm 0,075 mg, film-coated tablets

(desogestrel)

NL/H/5127/001/DC

Date: 22 November 2021

This module reflects the scientific discussion for the approval of Desogestrel Centrafarm 0,075 mg, film-coated tablets. The procedure was finalised at 7 April 2021. 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 Desogestrel Centrafarm 0,075 mg film-coated tablets, from Centrafarm B.V.

The product is indicated for: oral contraception.

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 Cerazette, 75 mcg, film-coated tablets which have been registered by NV Organon since 12 December 1997 through a national procedure (SE/H/0147/001).

The concerned member states (CMS) involved in this procedure were Denmark, Spain, Finland and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Desogestrel Centrafarm is a white, round film-coated tablet and contains as active substance 75 mcg of desogestrel. The tablets are packed in blisters of aluminium push-through foil and PVC/PVDC film.

The excipients are:
Tablet core - lactose monohydrate, maize starch, povidone (E1201), RRR-Alpha-tocopherol (E307), soy oil, silica colloidal anhydrous (E551), silica colloidal hydrated (E551) and stearic acid (E570)

Coating - hypromellose (E464), macrogol and titanium dioxide (E 171)

II.2 Drug Substance

The active substance is desogestrel, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder and is practically insoluble in water. Polymorphic forms of desogestrel were never detected during process development by the manufacturer.

The CEP procedure is used for the active substance. The CEP does not cover information concerning the stability of the drug 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

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. Batch analytical data demonstrating compliance with this specification have been provided for three commercial batches.

Stability of drug substance

Stability data on the active substance have been provided for five batches in accordance with applicable European guidelines demonstrating the stability of the active substance stored at 25°C/60% RH (three batches, 60 months), 30°/75% RH (two batches, 48 months), and 40°C/75% RH (six months). Based on the data submitted, a retest period could be granted of five years. Hygroscopicity and photostability study results for the drug substance support that no special storage conditions are required.

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. Formulation development and optimisation of type and amounts of excipients were carried out based on dissolution profile, content uniformity, stability and performance of manufacturing process. The master formula was selected based on its in vitro performance, manufacturability and stability in the proposed packing materials over the proposed shelf life. The addition of the antioxidant RRR-α-tocopherol was justified based on the composition of the reference product. The pharmaceutical development of the product has been adequately performed. The absence of dissolution studies at three pHs has been sufficiently justified based on the poor solubility and poor UV absorbance of the drug substance in water.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scale

batches and six full scaled batches, of which three after slight modification of the manufacturing process, in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. requirements, except for the coating system. However, all components of the coating system comply with the Ph. Eur. requirements. The absence of the functionality related characteristics tests of the excipients has been adequately justified. 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, identification of desogestrel, identification of tocopherol, desogestrel assay, tocopherol assay, desogestrel dissolution, desogestrel content uniformity, desogestrel related substances, and microbial control. 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 from seven batches, one pilot batch used in the bioequivalence study and six full scale batches, from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three pilot scaled and 3 production scaled batches stored at 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months), demonstrating the stability of the product. The conditions used in the stability studies are according to applicable European guidelines. In addition, stability studies on tablets packaged in bulk (double LDPE bag in GDPE container) were performed at 25°C/60% RH (12 months). Downward trend for α-tocopherol assay, and upward trends for specified, unspecified and total impurities were observed in all studies under all conditions. However, at long term and intermediate conditions all parameters stayed well within specification, whereas an out-of-spec results was seen for assay on one batch under accelerated condition. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage condition 'Do not store above 30°C' can be assigned. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when directly exposed to light. However, product packaged in blisters is stable when exposed to light. Therefore, the storage condition 'store in the original packaging to protect from light' has been implemented.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Desogestrel Centrafarm 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 Desogestrel Centrafarm 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 Cerazette 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

Desogestrel 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 Desogestrel Centrafarm 0,075 mg, film-coated tablets (Centrafarm B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Cerazette 75 mcg, film-coated tablets (NV Organon, Sweden).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single centre, randomised, single-dose, open-label, two-way crossover bioequivalence study was carried out under fasted conditions in 44 healthy female subjects, aged 18-45 years. Each subject received a single dose (0.075 mg) of one of the two desogestrel formulations. The tablet was orally administered with 200 ml water after an overnight fast of 12 hours. There were two dosing periods, separated by a washout period of 28 days.

Blood samples were collected at pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable.

Desogestrel may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of desogestrel. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Three subjects were excluded from analysis. One subject withdrew consent, one subject was withdrawn due to a positive serum pregnancy test and one due to a positive result for urine cotinine test. 41 Subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 3-keto desogestrel under fasted conditions.

Treatment N=41	AUC_{0-72} (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	5352.33 (1853.50)	843.28 (305.24)	1.25 (0.667 – 4.00)
Reference	5126.45 (1580.18)	823.88 (264.14)	1.25 (0.667 – 4.00)
***Ratio (90% CI)**	1.04 (0.99 – 1.10)	1.00 (0.92 – 1.10)	-
CV (%)	14.87	23.85	-

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Desogestrel Centrafarm is considered bioequivalent with Cerazette.

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 Desogestrel Centrafarm.

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

Important identified risks	- Venous thromboembolism - Arterial thromboembolism
Important potential risks	- None
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 Cerazette. 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 (PL) 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 PL was English. The test consisted of: a pilot test with two 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 PL 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

Desogestrel Centrafarm 0,075 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Cerazette 75 mcg, film-coated tablets. Cerazette 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 Desogestrel Centrafarm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 April 2021.

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/5127/001/IB/001	Change of product name in Finland	yes	01.11.2021	approved	Not applicable
NL/H/5127/001/IA/002	Change of address of batch releaser Centrafarm Services B.V, Netherlands	no	Submission planned for 31.12.2021	Not available	Not applicable