Public Assessment Report

Scientific discussion

Delamonie

75 microgram film-coated tablets

(Desogestrel)

DK/H/2442/001/DC

28 June 2016

This module reflects the scientific discussion for the approval of Delamonie. The procedure was finalised on 9 September 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Delamonie 75 microgram film-coated tablets, from Sandoz A/S.

The product is indicated for contraception.

A comprehensive description of the indications and posology is given in the SmPC.

Delamonie 75 microgram film-coated tablets is a progestogen-only pill, which contains the progestogen desogestrel. Like other progestogen-only pills, Delamonie tablets is best suited for use during breast feeding and for women who may not or do not want to use oestrogens. In contrast to traditional progestogen-only pills, the contraceptive effect of Delamonie tablets is achieved primarily by inhibition of ovulation. Other effects include increased viscosity of the cervical mucus.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Cerazette which has been registered in Sweden by N.V. Organon since 1997. In Denmark Cerazette has been registered by N.V. Organon since 1998.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each film coated tablet contains 75 microgram desogestrel.

The product is supplied in PVC-PVDC/Al Blisters in pack sizes of 1x28, 3x28, 6x28 and 13x28 tablets. However, not all pack sizes may be marketed.

The tablet core contains: Lactose monohydrate; Maize starch; Povidone K30; Silica colloidal hydrated; Silica colloidal anhydrous; RRR-α-tocopherol; Stearic acid and Soya-bean oil, refined.
The coating consists of: Hypromellose 2910; Macrogol 400 and Titanium Dioxide (E171).

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The manufacturer of the active substance, desogestrel, has obtained a Certificate of Suitability.

The control tests and specifications for drug substance product are adequately drawn up.

The analytical methods are in general performed according to Ph. Eur. However, the method for determination of particle size is an in-house method.

The re-test period is according to the CEP.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The low dose drug product is produced by a validated method.

The product specifications in general cover appropriate parameters for this dosage form.

Validations of the analytical methods have been presented. Batch analysis has been performed on six batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. A shelf-life of 36 months with the storage condition "Do not store above 30ºC. Store in the original package in order to protect from light" is approved.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of desogestrel are well known. As desogestrel is a widely used well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers several publications up to year 2008. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of desogestrel released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

IV. CLINICAL ASPECTS

IV.1 Introduction

Desogestrel is a well-known active substance with established efficacy and tolerability. As desogestrel is a widely used, well-known active substance, the MAH has not provided additional studies (apart from a supportive bioequivalence study referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers several publications up to year 2008. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Bioequivalence study
To support the application, the MAH submitted one single bioequivalence study under fasting conditions, in which Delamonie 75 microgram film-coated tablets was compared to Cerazette 75 microgram film-coated tablets, Organon Espanola, S.A., from the Spanish market.

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting with a wash out period of 29 days between the two administrations. 75 microgram was administered in each period.

A total of 44 female volunteers were dosed. 41 subjects completed the study and were included in the pharmacokinetic and statistical analyses.

Primary variables were $AUC_{0\text{-}72h}$ and C_{max}.

90% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed $AUC_{0\text{-}72h}$ and C_{max} should be within 80.00% to 125.00% in order to conclude bioequivalence.

Results

Table 1. Summary of pharmacokinetic parameters for 3-keto-desogestrel for each treatment (N=41)

Parameters		Test (Desogestrel (A)) Mean	SD	CV (%)	Reference (Cerazette® (B)) Mean	SD	CV (%)
$AUC_{0\text{-}72h}$	(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)	1.25	0.50	-	1.25	0.25	-

* Medians and interquartile ranges are presented.

Table 2. Ratios, 90% geometric confidence intervals and intra-subject CVs (%) for $AUC_{0\text{-}72h}$ and C_{max} for 3-keto-desogestrel (N=41)

	$AUC_{0\text{-}72h}$	C_{max}
Ratio[1]	104.18%	100.54%
90 % Geometric C.I.[2]	98.59 % to 110.09 %	92.09 % to 109.76 %
Intra-Subject CV	14.87 %	23.85 %

[1] Calculated using least-squares means according to the formula: $e^{(A-B)} X\ 100$.
[2] 90% Geometric Confidence Interval using ln-transformed data.

The 90% confidence interval for the ratio between test and reference were within the acceptance criteria 80.00-125.00% for $AUC_{0\text{-}t}$ and C_{max}.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study Delamonie 75 microg film-coated tablets is considered bioequivalent with Cezarette 75 microg film-coated tablets under fasting conditions.

The RMS 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.2 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 Delamonie.

The following summary list of safety concerns has been agreed with no additional pharmacovigilance or risk minimisation measures:

Table 1: Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	Disturbances in vaginal bleeding pattern Increase in blood pressure Risk of ectopic pregnancy
Important potential risks	Venous thromboembolic events Cerebrovascular accidents Breast cancer Abnormal liver function/liver cancer
Missing information	Use in adolescents below 18 years

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 language used for the purpose of user testing the PIL was English.
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.

The test consisted of a pilot test followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Delamonie 75 microgram film-coated tablets has a proven chemical-pharmaceutical quality and is comparable to Cerazette. 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.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that a marketing authorisation for Delamonie could be granted. The decentralised procedure was finalised on 9 September 2015. Delamonie was authorised in Denmark on 28 September 2015.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no routine PSURs are required for this product.

The date for the first renewal will be: 9 March 2020.

There were no post-approval commitments made during the procedure.