COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Ethinylestradiol/Dienogest Mithra 0.03 mg/2 mg, film-coated tablets

# (ethinylestradiol and dienogest)

# NL/H/5600/001/DC

# Date: 23 February 2023

**This module reflects the scientific discussion for the approval of Ethinylestradiol/Dienogest Mithra 0.03 mg/2 mg, film-coated tablets. The procedure was finalised at 6 September in Germany (DE/H/3129/001/DC). After a transfer on 1 April 2022, the current RMS is the Netherlands. 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 |
| EMA | European Medicines Agency |
| 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 |
| RMS | Reference Member State |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Ethinylestradiol/Dienogest Mithra 0.03 mg/2 mg tablets, in the treatment of

- Hormonal contraception
- Treatment of women with moderately severe acne who have no contraindications for treatment with oral contraceptives and after suitable local treatments have failed

is approved.

## I.1 About the product

This decentralised application concerns a generic version of a combined oral contraceptive containing 2 mg dienogest (DNG) and 0.03 mg ethinylestradiol (EE) per film-coated tablet, under the following trade names: Ethinylestradiol/Dienogest Mithra, Gamanogest, Bonadea, Kappanogest, Lamdanogest, Verezana, Velvet-ratiopharm 0,03 mg/2 mg Filmtabletten. The trade name Ethinylestradiol/Dienogest Mithra is used in this Assessment Report.
EE is a synthetic estrogen contained in most currently marketed combined oral contraceptives (COCs). DNG is a nortestosterone derivative and is unique as it contains a cyanomethyl group at position 17α. DNG shows antiandrogenic properties. It has been used as the progestogenic component of a combined oral contraceptive in the RMS since 1991. DNG is also approved as a monopreparation for the treatment of endometriosis (Visanne, NL/H/1569/001/DC) and in fixed combinations with estradiol for oral contraception (Qlaira, NL/H/1230/01/DC) and for endometrial protection during postmenopausal hormone therapy (e.g. Climodien/Lafamme, NL/H/248-249, 595, 652/001/MR).
The preparation applied for is a monophasic COC, given once daily at a fixed dose over the treatment cycle of 21 days, followed by a 7-day tablet-free period.
The therapeutic indications applied for are
- Hormonal contraception
Treatment of women with moderately severe acne who have no contraindications for treatment with oral contraceptives and after suitable local treatments have failed.
These therapeutic indications are identical with the therapeutic indications approved for the reference product Valette.

## I.2 General comments on the submitted dossier

The application is submitted under article 10(1), generic application of Council Directive 2001/83/EC, as amended, claiming to be a generic to the reference product Celimona film-coated tablets, Jenapharm, Germany, and Valette film-coated tablets, Jenapharm, Germany.
Celimona and Valette also contain 2 mg DNG and 0.03 mg EE per tablet. Celimona was approved in DE on 13 December 2000 for the therapeutic indication hormonal contraception (MA no. 38619.00.00). Valette was approved in DE on 5 August 2005 for the therapeutic indications hormonal contraception and treatment of women with moderate acne with no

contraindications for therapy with oral contraceptives and after failure of suitable topical treatments (MA no. 3001416.00.00).
With regard to the dossier, one pivotal bioequivalence study were submitted. The reference product used in these studies was Valette coated tablets, MA no. 3001416.00.00.
This approach is accepted, and no further clinical data are required.
The clinical overviews was well written and of acceptable quality.
Together with the submitted documentation the information given in the submitted dossier is sufficient for this generic application.

### I.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS 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.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

## II. QUALITY ASPECTS

### II.1 Introduction

The proposed medicinal product, Ethinylestradiol/Dienogest Mithra 0.03 mg/2.0 mg film coated tablets, is a fixed combination of the orally bio-active estrogen Ethinylestradiol (EE) and the progestogen Dienogest (DNG). The generic product is indicated for hormonal contraception (ATC code: G03AA) and, based on its anti-androgenic component in treatment of women with moderately severe acne, with no contraindications for therapy with oral contraceptives and after failure of appropriate topical treatments (ATC code: G03HB). The application is an abridged application according to Directive 2001/83/EC, article 10.1. The product is formulated as an immediate release tablet. Essential similarity is claimed between the generic product and the European reference product Celimona film-coated tablets, Jenapharm, Germany, and Valette film-coated tablets, Jenapharm, Germany.

### II.2 Drug Substance

**Ethinylestradiol (EE)** is the international non-proprietary name (INN) of the drug substance. It is also the name of the corresponding Ph. Eur. monograph (Ph. Eur., current edition, monograph no. 0140). For the drug substance, EE the applicant has submitted a Certificate of Suitability of the European Pharmacopoeia. The CEP involves an additional test for residual solvent by gas chromatography with a limit for toluene of NMT 750 ppm. Furthermore, any

other impurity than those mentioned in the monograph and detected by the method of the monograph for related substances have to be individually limited to NMT 0.10 %. A re-test period of 5 years with no special storage requirements is valid due to information of the CEP. Based on the applicant's responses on the RMS's questions raised on day 70 of the procedure the quality of ethinylestradiol is accepted as sufficiently controlled.
**Dienogest (DNG)** is the international non-proprietary name (INN) of the drug substance. DNG is not described in a pharmacopoeia. For the quality of DNG the applicant refers to the respective ASMFs of the two designated suppliers. Based on the applicant's responses on the RMS's questions raised on day 70 the quality of dienogest is accepted as sufficiently controlled.

## II.3 Medicinal Product

The pharmaceutical development on drug substances, excipients, tested formulations, impurities and dissolution has been sufficiently described. The discriminatory power of the dissolution method was investigated. However the robustness of the dissolution method is questionable and the applicant was requested to commit to perform further investigations regarding this. An adequate commitment has been provided on Day 160.
The product composition has been described sufficiently.
Acceptable validation data on three production scale batches manufactured in accordance with the final commercial manufacturing process have been provided. The batch analyses data together with the results obtained from stability testing confirm consistency and uniformity of the product based on the parameters tested and indicate the reproducibility of the manufacturing process for the drug product.
Except for lactose monohydrate all excipients are of non-animal origin. Adequate BSE/TSE respective origin declarations have been provided.
Both the release and shelf-life specification are mostly acceptable. An upper limit for resistance to crushing was requested by the RMS on day 70. Thereupon the applicant proposed an acceptable limit of NMT 60 N. However, this limit has not been implemented in the release and shelf life specification so far. Regarding dissolution the applicant was requested on day 70 to tighten the specification to NLT 80 % (Q) in 15 min for EE and DNG to be in compliance with the results obtained with the biobatch (> 85 % after 15 min for EE and DNG). Based on a detailed discussion provided, the applicant proposes a limit of NLT 80 % (Q) in 30 min for EE and DNG.
Potential impurities have been described acceptably.
Reference standards have been adequately characterised.
The EE/DNG-tablets for the commercial market are packed into thermoformed blister packages consisting of hard PVC/PVDC-foil and heat sealable aluminium foil.
LDPE-bags are used for bulk packaging. The provided specifications and information for the proposed container closure system are sufficient for the intended use.
The conditions used in stability studies are in accordance to those requested in the ICH stability guideline. The applicant provided further 6 months stability data. Overall 24 months long term data are available now demonstrating adequate compliance with the shelf life specification. Based on these data, the applicant´s proposal for a shelf-life of 24 months with specific storage conditions "Do not store above 30° C" is acceptable.

# III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of dienogest and ethinyl estradiol are well known. As both substances are widely used, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.
The nonclinical overview is dated 10 March 2010 and refers 36 publications up to year 2004.
The nonclinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.
There are no objections to approval of Ethinylestradiol/Dienogest Mithra from a non-clinical point of view.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

One randomized, open-label, two-way, crossover, controlled, single dose bioequivalence study in 24 healthy female volunteers between 18 and 50 years of age was submitted. The test product was Dienogest 2 mg/ Ethinylestradiol 0.03 mg Helm tablets (film-coated tablets. The reference product was Valette (Dienogest 2 mg/ Ethinylestradiol 0.03 mg tablets), Jenapharm, Germany. One tablet of test and reference each were administered in the fasting state, with a wash-out period of about one month.

The following results regarding the main pharmacokinetic parameters were reported:

**Table 1: Dienogest: Pharmacokinetic parameters (n=24) (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)**

| Treatment | AUC0-t ng/ml/h | AUC0-∞ ng/ml/h | Cmax ng/ml | tmax h | T1/2 h |
|---|---|---|---|---|---|
| Test | 642.95 ± 212.10 | 710.02 ± 234.75 | 62.69 ± 13.45 | 1.00 (0.52 – 3.50) | 9.69 ± 2.71 |
| Reference | 651.01 ± 245.73 | 715.91 ± 253.68 | 63.12 ± 15.23 | 1.00 (0.52 – 3.50) | 9.86 ± 2.81 |
| *Ratio (90 % CI) | 98.89% (93.27% to 104.85%) | 101.41% (95.44% to 107.75%) | 91.29% (85.99% to 96.92%) | | |
| CV (%) | 11.56% | 10.45% | 11.81% | | |

$AUC_{0-\infty}$ 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

**Table 2: Ethinylestradiol: Pharmacokinetic parameters (n=23 unless stated otherwise) (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)**

| Treatment | $AUC_{0-t}$ pg/ml/h | $AUC_{0-\infty}$ pg/ml/h | $C_{max}$ pg/ml | $t_{max}$ h | $T_{1/2}$ h |
|---|---|---|---|---|---|
| Test | 9.86 ± 2.81 | 878.81 ± 229.82** | 68.15 ± 20.05 | 1.50 (0.75 – 5.00) | 16.16 ± 3.18** |
| Reference | 745.26 ± 190.79 | 844.60 ± 206.23*** | 74.51 ± 19.86 | 1.50 (0.75 – 5.00) | 15.60 ± 3.56*** |
| *Ratio (90% CI) | 98.89% (93.27% to 104.85%) | 101.41% (95.44% to 107.75%) | 91.29% (85.99% to 96.92%) | | |
| CV (%) | 11.56% | 10.45% | 11.81% | | |

$AUC_{0-\infty}$ 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; **n=19; ***n=22

It is agreed that bioequivalence of test and Valette was demonstrated.

## IV.2 Pharmacovigilance System

The applicant has provided documents that set out a detailed description of the Helm system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided. The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union 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.

### IV.3 Risk Management Plan

The MAH has not submitted an RMP for this generic medicinal product containing dienogest and ethinylestradiol. This is endorsed by the RMS.
Reasoning:
According to the RMP guideline an EU-RMP should be submitted for a generic medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product. However, since no additional risk minimisation activities are required for the reference product, no RMP is required for the generic application.

### IV.4 Common renewal date

A proposed common renewal date of 5 years after finalisation of the procedure was accepted.

### IV.5 Legal status

Medicinal product subject to medical prescription

### IV.6 User testing

It is agreed that the user testing was successful. No changes of the PL are required.

## V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bioequivalence of Ethinylestradiol/Dienogest Mithra to the reference product Valette (Jenapharm, Germany) was shown. The SPC and PL were revised according to RMS comments and are acceptable. In consequence, approval of the generic product Ethinylestradiol/Dienogest Mithra is recommended."
The application is approved. For intermediate amendments, see the current product information.

## 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 |
|---|---|---|---|---|---|
| - | - | - | - | - | - |