COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Zoanne 2.5 mg/1.5 mg, film-coated tablets

(nomegestrol acetate and estradiol hemihydrate)

NL/H/5401/001/DC

Date: 26 Augustus 2022

This module reflects the scientific discussion for the approval of Zoanne 2.5 mg/1.5 mg, film-coated tablets. The procedure was finalised on 22 June 2022. 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 Zoanne 2.5 mg/1.5 mg, film-coated tablets, from Mylan Healthcare B.V.

The product is indicated for oral contraception.

The decision to prescribe this product should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with this product compares with other combined hormonal contraceptives (CHCs) (see SmPC sections 4.3 and 4.4).

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 reference product Zoely 2.5 mg/1.5 mg, film-coated tablets which has been registered in Ireland since 27 July 2011 by Theramex Ireland Limited. Zoely is authorised in the EEA via a centralised procedure (EMEA/H/C/001213), according to Article 10b of Directive 2001/83/EC – fixed combination application.

The concerned member state (CMS) involved in this procedure was Denmark.

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

II. QUALITY ASPECTS

II.1 Introduction

The drug product comes in blisters of 28 tablets, 24 white active and 4 green placebo tablets. Each white to off-white active tablet contains 2.5 mg nomegestrol acetate and 1.5 mg estradiol (as hemihydrate). Each green placebo tablet contains no active substances.

Active - Zoanne 2.5 mg/1.5 mg are white to off-white, round, biconvex film-coated tablets with bevelled edge, debossed with 'M' on one side and 'NE' on the other side, with a diameter of approximately 5.5 mm.

Placebo - Mottled green, round, biconvex uncoated tablet, debossed with 'I' on one side and plain on the other side with a diameter of approximately 5.5 mm.

The film-coated tablets are packed in PVC-Alu and PVC/PVdC-Alu blister packs containing 28 tablets (24 white active film-coated tablets and 4 green placebo uncoated tablets).

The excipients are:
Active film-coated tablet (white)
Tablet core - lactose monohydrate, microcrystalline cellulose, crospovidone, hypromellose, talc, colloidal silicon dioxide and magnesium stearate.
Tablet coating- polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 and talc.

Placebo uncoated tablet (green)
Lactose monohydrate, yellow iron oxide (E172), brilliant blue FCF (E133), polacrilin potassium and magnesium stearate.

II.2 Drug Substances

The active substances are nomegestrol acetate and estradiol hemihydrate, both established active substances described in the European Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for both active substances. 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.

Nomegestrol acetate
Nomegestrol is a white or almost white crystalline powder and is practically insoluble in water. Nomegestrol acetate, as steroids, shows specific rotation due to the presence of six asymmetric carbons. It does exhibit polymorphism, there are several forms known. The manufacturer ensures consistently providing the stable single crystalline form due to a reproducible crystalline process and control of the polymorphic form can be excluded from the control strategy.

It is a highly selective progestogen derived from the naturally occurring steroid hormone, progesterone. Nomegestrol acetate has a strong affinity for the human progesterone receptor and has an anti-gonadotropic activity, a progesterone receptor-mediated anti-oestrogenic activity, a moderate anti-androgenic activity, and is devoid of any oestrogenic, androgenic, glucocorticoid or mineralocorticoid activity.

<u>Manufacturing process</u>
A CEP has been submitted; therefore no details on the manufacturing process have been included.

<u>Quality control of drug substance</u>
The active substance specification is considered adequate to control the quality and meet the requirements of the monograph in the Ph.Eur and the CEP, with additional requirements

for residual solvents and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Estradiol hemihydrate
Estradiol hemihydrate is a crystalline powder or crystals and is practically insoluble in water. Zoanne contains 17β-estradiol, a natural oestrogen identical to the endogenous human 17β-estradiol. Estradiol exists as hemihydrate, which contains between 2.9 % and 3.5 % water and it does exhibit polymorphism. It forms two unstable anhydrous forms, polymorph I and II, which are readily transformed into the hemihydrate under the influence of atmospheric moisture. The manufacturer ensures consistently providing the estradiol hemihydrate which is the stable form, hence control of the polymorphic form can be excluded from the control strategy.

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 meet the requirements of the monograph in the Ph.Eur and the CEP, with additional requirements for residual solvents and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substances
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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. The development of the product has been described, the choice of excipients is justified and their functions explained for the active and placebo tablets. The dissolution method and its discriminatory power has been sufficiently addressed. The comparative *in vitro* dissolution tests complementary to the bioequivalence study demonstrated similarity. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consist of mixing, granulation, milling and sizing, blending, lubrication, compression and film-coating. Due to the low active substance content, it is regarded as non-standard process. The manufacturing process has been validated for a batch of the active and placebo tablets according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

Except for the film coating, Opadry II white 85F18422 and FD&C Blue No.1, the excipients comply with Ph.Eur./USP-NF requirements. 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 product specification of the active tablets includes tests for description, dimensions, identification, dissolution, uniformity of dosage units (content uniformity), assay, related substances, colour identification, water content and microbiological purity Except for related substances and water content the release and shelf-life specifications are identical. The product specification of the active tablet is acceptable. The product specification of the placebo tablets includes tests for description, dimensions, average weight, absence of hormones, water content, colour identification, disintegration and microbiological purity. The product specification of the placebo tablets is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are accordance with applicable European guidelines (ICH stability guidelines). The batches were stored in PVC-Alu blisters, PVC/PVdC-Alu blister and LDPE bags (bulk packaging) Photostability studies showed that the product is stable when exposed to light. Based on the submitted stability data, a shelf life of 18 months was granted. No specific storage conditions need to be included in the SmPC or on the label.

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 Zoanne has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Zoanne 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 Zoely 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

Nomegestrol acetate and estradiol hemihydrate are well-known active substances 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 Zoanne 2.5 mg/1.5 mg, film-coated tablets (Mylan Healthcare B.V., The

Netherlands) is compared with the pharmacokinetic profile of the reference product Zoely 2.5 mg/1.5 mg, film-coated tablets (Theramex Ireland Limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference product 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-dose, randomised, blinded, two-period, two-treatment, two-sequence, crossover, oral bioequivalence study was carried out, under fasted conditions in 54 post-menopausal (12 months of spontaneous amenorrhea or 6 months postsurgical bilateral oophorectomy with or without hysterectomy) healthy female subjects, aged 45-60 years. Each subject received a single dose (2.5 mg/1.5 mg of the nomegestrol acetate/estradiol). The tablet was orally administered with 240 mL water (swallow whole tablet, not be broken, chewed or crushed) after overnight fast of at least 10 hours prior to dosing and until 4 hours post dose. Drinking water was not permitted 1 hour before and 1 hour after dosing. The study was conducted in two groups. There were two dosing periods, separated by a washout period of 29 days for group I and 28 days for group II. In group-I, thirty subjects were enrolled. In group-II, twenty-four subjects were enrolled for a total of 54 subjects.

Blood samples were collected at 0.00 hours (pre-dose), and 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the product.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC of the applied product, no clinically relevant effect of food was observed on the bioavailability of nomegestrol acetate or estradiol.

The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98-Rev 01 – Jan. 2010 Note for Guidance on the investigation of bioavailability and bioequivalence. The dissolution profiles can be considered similar without further mathematical calculations.

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

A total of 54 subjects were enrolled in this study, of which 50 subjects were eligible for pharmacokinetic analysis. Four subjects dropped out. One subject was withdrawn due to an adverse event (vomiting) during period 2. Two subjects were withdrawn from the study due

to personal reasons before period 2 check in. One subject did not report to the facility for period 2 check in due to personal reasons. The plasma concentration data and pharmacokinetic parameters from drop-out subjects have not been determined and are therefore not available. Not analysing the samples of these subjects is considered acceptable.

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

Treatment N=50	AUC_{0-t} (h.pg/mL)	$AUC_{0-\infty}$ (h.pg/mL)	C_{max} (pg/mL)	t_{max} (h)
Test	118898 ± 28014	Not reported	9077 ± 2720	2.50 (1.00 – 5.00)
Reference	111260 ± 25332	Not reported	7953 ± 2115	2.50 (1.00 – 6.00)
***Ratio (90% CI)**	1.07% (1.03 – 1.10)	--	1.12% (1.05 – 1.20)	--
CV (%)	10.0	--	19.7	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) of estradiol (test: n = 50; reference: n = 50 for AUC_{0-t}, C_{max} and t_{max}, and n = 47 for $AUC_{0-\infty}$, ratios with and without subjects with pre-dose levels >5% of C_{max} or C_{max} in the first sampling point).

Treatment	AUC_{0-t} (h.pg/mL)	$AUC_{0-\infty}$ (h.pg/mL)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)
Test	1225 ± 561	1330 ± 611	44.9 ± 18.9	10.00 (0.50 – 24.00)	15.810
Reference	1093 ± 465	1231 ± 505	40.2 ± 15.2	10.00 (4.00 – 72.00)	15.500
***Ratio (90% CI) (N=50)**	109.31% (101.16 – 118.12)	--	110.91% (102.84 – 119.61)	--	--
CV (%)	23.4	--	22.8	--	--
***Ratio (90% CI) (N=45)**	1.10% (1.02 – 1.20)	--	1.09% (1.01– 1.18)	--	--
CV (%)	23.1	--	22.4	--	--

$AUC_{0-\infty}$	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
CV	coefficient of variation

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

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 Zoanne.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Depression/Depressed mood • Venous thromboembolic events • Arterial thromboembolic events
Important potential risks	• Cholelithiasis/Cholecystitis/Elevated hepatic enzymes • Meningioma
Missing information	• Safety in post-menarcheal adolescents • Safety in women during pregnancy

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 Zoely. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Zoely 2.5 mg/1.5 mg, film-coated tablets (EU/1/11/690) for content and to Abevmy 25 mg/ml concentrate for solution for infusion (EU/1/20/1515) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Zoanne 2.5 mg/1.5 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Zoely 2.5 mg/1.5 mg, film-coated tablets. Zoely 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 Zoanne with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 June 2022.

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