Public Assessment Report

Scientific discussion

Femilux 0.02 mg/3 mg film-coated tablets

(Ethinylestradiol/Drospirenone)

NL/H/2899/001/DC

Date: 14 January 2015

This module reflects the scientific discussion for the approval of Femilux 0.02 mg/3 mg film-coated tablets. The procedure was finalised on 21 November 2013. 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 Femilux 0.02 mg/3 mg film-coated tablets from Egis Pharmaceuticals Plc

The product is indicated for oral contraception.
A comprehensive description of the indication and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Yaz 24+4, film-coated tablets 0.02 mg/3 mg (NL License RVG 33842) which has been registered in the Netherlands by Bayer B.V. since 29 June 2007. Subsequently it was part of MRP NL/H/1269/001.
The first drospirenone/ethinylestradiol authorisation was granted on 7 March 2000 for the product Yasmin, containing 3 mg drospirenone and 0.03 mg ethinylestradiol (NL/H/215/001).

The concerned member states (CMS) involved in this procedure were Czech Republic, Hungary, Poland and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

The medicinal products consist of blisters filled with 24 active tablets and 4 placebo tablets. Femilux 0.02 mg/3 mg are round, pink film-coated tablets. The placebo tablets are white, film-coated tablets without any active substance.

The pack is a clear to slightly opaque transparent PVC/PVDC/Al blister.

The excipients in the active tablet are:
Tablet core - lactose monohydrate, maize starch, pregelatinised starch (maize), crospovidone type B, povidone K-30 (E1201), polysorbate 80 (E433), magnesium stearate (E470b)
Coating - poly (vinyl alcohol), titanium dioxide (E171), macrogol 3350, talc (E553b), yellow iron oxide (E172), red & black iron oxide (E172)

The placebo tablets contain lactose anhydrous, povidone K30, magnesium stearate and Opadry® II White (consisting of poly (vinyl alcohol), titanium dioxide, macrogol 3350 and talc).

II.2 Drug Substances

Ethinylestradiol
The active substance ethinylestradiol is an established active substance, described in the European Pharmacopoeia (Ph.Eur.). It is a white or slightly yellowish-white crystalline powder, which is practically insoluble in water and freely soluble in alcohol. It dissolves in dilute alkaline solutions. Ethinylestradiol exhibits only one not solvated polymorphic form.

The CEP procedure is used for the active substance ethinylestradiol. 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 European Pharmacopoeia.

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

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. and the CEP. An additional test for one residual solvent is included. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data have been provided.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Drospirenone
The active substance drospirenone is an established active substance, described in the Ph.Eur. It is a white or almost white powder. Water solubility is 10.9 mg/l. Drospirenone does not show polymorphic forms. The CEP procedure is used for this active substance.

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

Quality control of drug substance
The drug substance specification is based on the Ph.Eur. monograph and the CEP with additional tests for one residual solvent. The specifications are acceptable in view of the route of synthesis and the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 4 years when stored under the stated conditions. No special storage conditions are required. The assessment was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The product development objective was to develop film-coated tablets that would be bioequivalent to the medicinal product Jasminelle®, having the same qualitative and quantitative composition in drug substances per tablet and the same pharmaceutical form.
A water based wet granulation process was tried and experimental batches were tested and dissolution profiles were compared to the dissolution profile of the reference product.
Dissolution profiles at three different pH values were determined for test and reference batches used in the bioequivalence study. Similarity of the test product to the Dutch reference product Yaz® (24+4; Bayer B.V., RVG 33842) has also been proven. Additionally, a comparison of three industrial validation batches against the bioequivalence pilot batch and both reference products (Jasminelle® and Yaz®) was performed. It was shown that all profiles are comparable. Sufficient in-vitro data have been presented.
A compatibility study was performed to describe potential interactions between the individual excipients and the active drug substances. The container closure system (PVC-PVdC/aluminium blisters) is usual for this type of dosage form.

Manufacturing process
The drug product is manufactured by wet granulation. The process consists of blending, granulation, drying, milling, tablet compression and coating. The in-process controls for the manufacturing process of the active tablets are acceptable. The manufacturing process has been adequately validated according to relevant European Guidelines. For the placebo tablets, a direct compression method has been described. Adequate information on in-process controls has been provided. No process validation is required for the placebo tablets.

Control of excipients
All excipients are tested in accordance with their respective Ph.Eur. monograph, except for Opadry® II Pink and Opadry® II White, which are tested according to in-house procedures. The specifications are acceptable.

Quality control of drug product
The active drug product specification includes tests for appearance, identification (release only), dissolution, assay, related substances, content uniformity (release only), residual solvents (release only) and microbial control. For appearance, dissolution, drospirenone assay, drospirenone related

substances and microbial control, the shelf-life specifications are the same as the release specifications. For assay of ethinylestradiol, the shelf-life specification is wider than the release specification, which is supported by stability data.
The placebo drug product specification includes tests for appearance, average weight, disintegration time and microbial control. The shelf-life specifications are the same as the release specifications.
The analytical methods have been adequately described and validated. The HPLC methods for assay and related substances are considered to be stability indicating.
Batch analytical data for two pilot batches and three industrial batches of each of the strengths of the drug product have been provided, as well as data for one pilot batch of the placebo tablets, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the placebo tablets have been provided for one pilot-scale batch, stored at 25°C/60% (36 months) and 40ºC/75% RH (6 months). The parameters appearance, disintegration time and microbial control remained within specifications. In view of the stability data presented, a shelf-life of 36 months for the placebo tablets is acceptable.
Stability data on the active drug product have been provided on two pilot-scale and three commercial-scale batches of each strength. The batches were stored at 25°C/60% RH (36 months for the pilot-scale and 12 months for the commercial-scale batches), 30°C/65% RH (12 months for two commercial scale batches) and 40°C/75%RH (6 months for all batches). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC-Al blisters.
A photostability study in compliance with the NfG on Photostability Testing has been performed, which shows that the product is not sensitive to light. In view of the provided stability data, the claimed shelf-life of 36 months and the proposed storage conditions “Store below 30ºC” were granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE declarations have been provided for lactose monohydrate and lactose anhydrous, as they are of animal origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Femilux film-coated tablets have 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 Femilux 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 Yaz 24+4, which is available on the European market. Reference is made tot 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

Drospirenone and ethinylestradiol 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Femilux 0.02 mg/3 mg (Egis Pharmaceuticals Plc, Hungary) is compared with the pharmacokinetic profile of the reference product Jasminelle 3.0 mg/0.02 mg film-coated tablets (Schering S.A.S, France).

The choice of the reference product
The choice of the reference products in the bioequivalence studies 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.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies
Bioequivalence study I – 3 mg/0.02 mg strength
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy females of childbearing potential, aged 20-43 years old. Each subject received a single dose of three tablets (3 x 3 mg/0.02 mg) of one of the 2 drospirenone/ethinylestradiol formulations. The tablets were orally administered with 240 ml water after a fasting period of at least 10 hours. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120 hours after administration of the products.

The design is acceptable for this kind of application, the wash-out of 28 days is sufficient and the sampling period long enough. Furthermore, the sampling scheme is adequate to estimate pharmacokinetic parameters. The administration of 3 tablets was considered necessary to achieve measurable plasma ethinylestradiol levels and justified by dose-linearity of drospirenone (1–10 mg) and Ethinylestradiol (20–60 µg). This is acceptable.

Results
Two subjects withdrew and did not show up for the second period of the study. Therefore a number of 32 subjects completed the study. However, one subject was excluded from the analysis since pre-dose concentrations of >5% of C_{max} were observed in both periods for both compounds. Statistical analysis was performed with 31 subjects.

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

Treatment N=31	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1.3 ± 0.3	1.4 ± 0.4	85 ± 15	1.75	32.7
Reference	1.3 ± 0.3	1.4 ± 0.4	85 ± 17	1.75	31.9
***Ratio (90% CI)**	1.00 (0.97-1.02)	1.00 (0.98-1.02)	1.01 (0.94-1.07)	--	--

CV (%)	5.1	5.1	14.9	--	--

$AUC_{0-\infty}$ 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. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ethinylestradiol under fasted conditions.

Treatment N=31	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1.4 ± 0.3	1.6 ± 0.3	142 ± 29	1.75	32.7
Reference	1.5 ± 0.3	1.7 ± 0.3	147 ± 29	1.75	31.9
***Ratio (90% CI)**	0.95 (0.90-0.99)	0.95 (0.90-0.99)	0.96 (0.91-1.02)	--	--
CV (%)	11.1	10.5	13.8	--	--

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of drospirenone and ethinylestradiol under fasted conditions, it can be concluded that Femilux 0.02 mg/3 mg and Jasminelle, 3.0 mg/0.02 mg, film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A significant treatment effect was observed for the $AUC_{(0-\infty)}$ of ethinylestradiol and a significant period effect for the $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of drospirenone. The observed treatment effect is considered due to the high power of the study and therefore clinically not relevant since bioequivalence has been shown. The period effect for drospirenone is neither judged to influence the conclusion of the study since only 1 case of a pre-dose level was detected and therefore no carry-over effect could be concluded.

Drospirenone/ethinylestradiol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of the active substances. 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.

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 Femilux 0.02 mg/3 mg film-coated tablets.

Summary table of safety concerns as approved in RMP

Important identified risks	Venous thromboembolism, Arterial thromboembolism Breast cancer Benign and malignant liver tumours Disturbances of liver function Pancreatitis Increased blood pressure Effect on hereditary angioedema
Important potential risks	Cervical cancer Worsening of endogenous depression Crohn's disease and ulcerative colitis Insulin resistance Hyperkalemia
Important missing information	-

The safety concerns included in the RMP are considered appropriate. The member states agreed that routine pharmacovigilance activities and routine risk minimisation activities are considered sufficient for this product.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Yaz® 24+4. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the two products is similar to the pharmacokinetic profile of these reference products. Risk management is adequately addressed. This generic medicinal products can be used instead of its reference product.

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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results of the first round of testing met the study objectives. Therefore, no amendments to the package leaflet were considered necessary. Also the results of the second round of testing met the study objectives. The readability test has been sufficiently performed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Femilux 0.02 mg/3 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Yaz 24+4, film-coated tablets 0.02/3 mg. Yaz is a well-known medicinal products with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of the reference product. The SmPC, package leaflet and labelling are in the agreed templates.

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 Femilux 0.02 mg/3 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 21 November 2013.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached