PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Levonorgestrel/ethinylestradiol Famy 0.10/0.02 mg coated tablets
Famy Care Europe Ltd., United Kingdom

levonorgestrel/ethinylestradiol

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2167/001/DC
Registration number in the Netherlands: RVG 108781

25 January 2012

Pharmacotherapeutic group:	hormonal contraceptives for systemic use; progestogens and estrogens, fixed combinations
ATC code:	G03AA07
Route of administration:	oral
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of authorisation in NL:	27 December 2011
Concerned Member States:	Decentralised procedure with DE, IE, IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Levonorgestrel/Ethinylestradiol Famy 0.10/0.02 mg, tablets from Famy Care Europe Ltd. The date of authorisation was on 27 December 2011 in the Netherlands. The product is indicated for oral contraception.

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

The active ingredients, levonorgestrel (LNG) and ethinylestradiol (EE) are well-known. LNG is a so-called second generation progestogen, which belongs to the gonane group derived from the C-19 nortestosterone. LNG possesses progestogenic activity. EE is a synthetic steroid with high oral estrogenic potency known since more than 60 years and is used as the estrogen component in most combined oral contraceptives (COCs). The present preparation is a monophasic COC. Due to the low estrogen content, the preparation belongs to the so-called low-dose COCs (i.e., with an EE content of no more than 35 µg per tablet).

The contraceptive effect of combined oral contraceptives (COCs) is based on the interaction of various factors. The most important of these factors are the inhibition of ovulation and changes in the cervical mucus.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Miranova tablets, which has been registered in Finland by Bayer Schering Pharma Oy since 18 January 1999 (original product). In the Netherlands, Miranova coated tablets (NL License RVG 30862) has been registered by Bayer B.V. since 11 February 2005 through procedure FI/H/0333/001/MR. In addition, reference is made to Miranova authorisations in the individual member states (reference product).

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

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Miranova, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB 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.

Active substances

Levonorgestrel
The active substance levonorgestrel is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white crystalline powder, which is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in alcohol.

The CEP procedure is used for the active 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 new 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 specifications are in line with the Ph.Eur. and the CEP. Additional specifications have been laid down by the MAH. Overall, the specifications are acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specifications were provided for three commercial batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Ethinylestradiol
The active substance ethinylestradiol is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or slightly yellowish-white, crystalline powder. Ethinylestradiol is freely soluble in ether, ethanol, acetone and dioxane, soluble in alkali hydroxide solutions, sparingly soluble in chloroform and practically insoluble in water. Ethinylestradiol is known to show polymorphism. The drug substance used is the anhydrate form.

The CEP procedure is also 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 specifications are in line with the Ph.Eur. and the CEP. Additional specifications have been laid down by the MAH. Overall, the specifications are acceptable in view of the various European

guidelines. Batch analytical data demonstrating compliance with the drug substance specifications were provided for three commercial batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition
Levonorgestrel/Ethinylestradiol Famy 0.10/0.02 mg is a round, pink, 5.60 mm coated tablet.

The coated tablets are packed in PVC/PVDC/Aluminium blisters of 21 tablets.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, crosscarmellose sodium, povidone, magnesium stearate VG
Coating - povidone, purified talc, glycerol, 2-propanol Extra pure, sucrose, calcium carbonate, macrogol 6000, titanium dioxide (E171), ferric oxide (red) (E172), ferric oxide (yellow) (E172), carnauba wax.

Pharmaceutical development
The development of the product was described, the choice of excipients was justified and their functions were explained. Formulation development was based on the composition and dissolution characteristics of the reference product. The composition of the generic product was adapted for increased disintegration. Well-known excipients are used. A direct compression approach with ordered mixing was chosen for the manufacturing process. Comparative *in vitro* dissolution data of the generic and reference product are not sufficient to demonstrate bioequivalence. However, the *in vitro* dissolution data are considered to be of secondary importance to the *in vivo* data.
The pharmaceutical development was described in sufficient detail.

Manufacturing process
The manufacturing process consists of dispensing, sifting, inactive bulk mixing, drug premixing, blending, lubrication, compression, preparation of the coating suspensions, coating and packaging. The manufacturing process was adequately validated according to relevant European guidelines. As the drug product corresponds to a specialised dosage form due to the very low drug content, full-scale validation data is required. Process validation data on the product was presented for three full-scale batches.

Control of excipients
With the exception of ferric oxide red and yellow, all excipients comply with the Ph.Eur. The colourants comply with the USP-NF. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification of the drug substances and colouring agents, water content, dissolution, assay, related substances, residual solvents, and microbial contamination. The release and shelf life limits differ with regard to water content and related substances.
The analytical methods were adequately described and validated.
Batch analytical data from the proposed production site were provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product was provided on three pilot-scale batches stored at 25°C/60% RH (twelve months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed commercial packaging. No significant changes were observed. On the basis of the provided eighteen months stability data, the claimed shelf life of 24 months is acceptable. No temperature storage condition is needed. A photostability study demonstrated that the drug product is not photosensitive. An in-use stability study of 1 month

demonstrated that the drug product packed in a blister can be stored outside the pouch. The shelf life that can be granted is 24 months without special storage conditions when packed in the PVC/PVDC-Al blisters.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal origin used in the manufacture of the drug product. A statement of the supplier declaring compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products was provided.

II.2 Non-clinical aspects

This product is a generic formulation of Miranova, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
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 levonorgestrel or ethinylestradiol 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.

II.3 Clinical aspects

Levonorgestrel and ethinylestradiol are well-known active substances with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Levonorgestrel/Ethinylestradiol Famy 0.10/0.02 mg (Famy Care Europe Ltd., UK) is compared with the pharmacokinetic profile of the reference product Miranova tablets (Bayer Schering, Germany).

The choice of the reference product
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.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy female subjects, aged 20-35 years. Each subject received two tablets (2 x 0.10/0.02 mg) of one of the 2 levonorgestrel/ethinylestradiol formulations. The tablets were orally administered with 240 ml water after an overnight fast of at least 10 hours. No other drinks were allowed 1 hour before dosing and 1 hour after dosing. Meals were provided 4 and 8 hours upon administration of the medicinal products. 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, 2.25, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

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.
As the half life for levonorgestrel is about 40–50 hours, calculation of the AUC0-inf is considered not necessary. According the guideline blood sampling till 72 hours post dosing should be adequate to describe the pharmacokinetic profile for bioequivalence testing.

Results

Two subjects dropped as they did not show up for the second period. Pharmacokinetic and statistical analysis was performed with data on 54 subjects for levonorgestrel and 26 subjects for ethinylestradiol.

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

Treatment N=54	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	87.3 ± 41.1	--	5.93 ± 2.43	1.75 (1.0 – 5.0)	49.5 ± 20.8
Reference	88.6 ± 46.8	--	6.90 ± 2.95	1.25 (0.75 – 3.5)	53.8 ± 29.1
***Ratio (90% CI)**	1.01 (0.95 – 1.07)	--	0.86 (0.81 – 0.91)	--	--
Intra subject CV (%)	19.2	--	18.5	--	--

$AUC_{0-\infty}$ 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=26	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	786 ± 402	967± 516	79.9 ± 24.6	1.87 (1.0 – 2.5)	18.2 ± 7.8
Reference	766 ± 388	920 ± 460	80.9 ± 25.3	1.75 (1.0 – 3.0)	16.8 ± 8.0
***Ratio (90% CI)**	1.03 (0.97–1.10)	1.04 (0.98–1.11)	0.99 (0.94–1.05)	--	--
Intra-subject CV (%)	13.8	12.2	12.2	--	--

$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ (EE only) 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 LNG and EE under fasted conditions, it can be concluded that Levonorgestrel/Ethinylestradiol Famy 0.10/0.02 mg and Miranova tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

LNG and EE may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of LNG and EE. 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.

Extrapolation of results
The bioequivalence study has been performed with two tablets instead of one. The results of the bioequivalence study with administration of a single dose with two tablets can be extrapolated to the single-dose situation with one tablet.

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).

Risk management plan
The combination of levonorgestrel and ethinylestradiol was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of LNG+EE can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Miranova (FI/H/333/001) and the EU CSP of levonorgestrel/ethinylestradiol approved in April 2011 with the PSUR worksharing DK/H/PSUR/0054/001.

Readability test
The package leaflet has been evaluated via a user consultation study. Instead the MAH provided a bridging report with reference to the succesful user test for tablets containing levonorgestrel 150 microgram and ethinylestradiol 30 microgram. The text is nearly the same. The layout of the daughter PL is identical to the parent PL.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Levonorgestrel/Ethinylestradiol Famy Care 0.10/0.02 mg coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Miranova tablets. Miranova 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, 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 Levonorgestrel/Ethinylestradiol Famy 0.10/0.02 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 October 2011. Levonorgestrel/Ethinylestradiol Famy 0.10/0.02 mg coated tablets was authorised in the Netherlands on 27 December 2011.

The date for the first renewal will be: 28 October 2016.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to revise the limits for dissolution based on the trend data of commercial batches.
- The MAH committed to compare the dissolution profiles of the first three commercial validation batches to the generic biobatch.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
COC	Combined Oral Contraceptive
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EE	Ethinylestradiol
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
LNG	Levonorgestrel
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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