CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Zulima 150/30 micrograms, film-coated tablets
Laboratorios León Farma, S.A., Spain

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/2650/001/DC
Registration number in the Netherlands: RVG 111873

5 November 2013

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:	24 October 2013
Concerned Member States:	Decentralised procedure with CZ, DE, ES, FR, RO, SK
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 Zulima 150/30 micrograms, film-coated tablets from Laboratorios León Farma, S.A. The date of authorisation was on 24 October 2013 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. Levonorgestrel is a so-called second generation progestogen, which belongs to the gonane group derived from the C-19 nortestosterone. Levonorgestrel possesses progestogenic activity. Ethinylestradiol is a synthetic steroid with high oral estrogenic potency and is used as the estrogen component in most combined oral contraceptives (COCs). 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 Microgynon 30, 0.15 mg/0.03 mg, coated tablets (NL License RVG 08204) which has been registered in the Netherlands state by Bayer B.V. since 5 September 1974 (original 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 Microgynon 30, 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

Levonorgestel
The active substance levonorgestel is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to almost white crystalline powder. Levonorgestrel is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in ethanol.

The CEP procedure is used for this 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 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 fully in line with the currently valid Ph.Eur. monograph for levonorgestrel and the additional tests laid down in the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for one full-scale batch.

Stability of drug substance
The active substance is stable for 4 years 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. The active substance is a white or slightly yellowish-white, crystalline powder. Ethinylestradiol is practically insoluble in water, freely soluble in alcohol. It dissolves in dilute alkaline solutions. Two polymorphic forms of ethinylestradiol are known, *i.e.* an anhydrate and a solvate. The anhydrate form is used.

The CEP procedure is used for ethinylestradiol.

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 currently valid Ph.Eur. monograph for ethinylestradiol

and the additional tests laid down in the CEP. The analytical methods used are in accordance with the CEP (and therefore with the current Ph. Eur.). Batch analytical data demonstrating compliance with the drug substance specification 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.

Medicinal Product

Composition
Zulima 150/30 micrograms is a yellow, round tablet, with a diameter of 6 mm and thickness less than 4 mm approximately.

The film-coated tablets are packed in blisters of aluminium push-thru foil and PVC/PVDC film.
The excipients are:
Tablet core - lactose monohydrate, povidone K30, crospovidone type A, magnesium stearate
Coating - partial hydrolized polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc (E553b), iron oxide yellow (E172)

Pharmaceutical development
The pharmaceutical development of the product has been adequately described. All excipients used are well-known and commonly used pharmaceutical ingredients for tablet production. The function of each excipient has been adequately described. The test and reference products used in the bioequivalence study are acceptable. The results of dissolution testing at three pH values show that all the profiles are considered similar to the reference product.

Manufacturing process
The manufacturing process is considered to be non-standard process due to the low content of active substances. The process consists of mixing, blending an compression. The tablets are then coated and packed in PVC/PVDC/Alu blister packs. Adequate process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with the Ph.Eur., except for the coating mixture Opadry Yellow. The provided specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance,
identification of levonorgestrel and ethinylestradiol, water content, levonorgestrel assay, ethinylestradiol assay, levonorgestrel dissolution, ethinylestradiol dissolution, levonorgestrel content uniformity, ethinylestradiol uniformity, levonorgestrel related substances, ethinylestradiol related substances and microbial control. The release and end of shelf-life specifications are not identical. The lower levels of the assay limits for both drug substances are widened for the end of shelf-life specifications, and the limits for related substances are widened. This is considered to be acceptable in view of the stability data. The in-house methods have been adequately described and validated. Batch analysis results for three full-scale batches have been provided, demonstrating compliance with the proposed release specifications.

Stability of drug product
Stability data on the product has been provided on three full-scale batches at 25°C/60%RH (18 months), 30°C/70%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the dosage form proposed for marketing. The tablets are considered photostable based on results of photostability testing.
The proposed shelf life of 24 months is acceptable. The storage conditions are "Do not store above 30ºC'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The only excipient used that could have any risk of BSE is lactose anhydrous. The lactose used is sourced from healthy animals in the same conditions as milk collected for human consumption. BSE/TSE certificates have been provided.

II.2 Non-clinical aspects

This product is a generic formulation of Microgynon 30, which is available on the European market. 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.

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 substance 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 in which the pharmacokinetic profile of the test product Zulima 150/30 micrograms (Laboratorios León Farma, S.A., Spain) is compared with the pharmacokinetic profile of the reference product Microgynon 30 tablets (Bayer Schering Pharma AG, 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.
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 40 healthy female subjects, aged 22 - 43 years. Each subject received a single dose (0.15 mg/0.03 mg) of one of the 2 levonorgestrel/ethinylestradiol formulations. The tablet was orally administered with 240 ml water after an overnight fast. 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 and 72 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable.

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

One subject did not complete the study due to personal reasons. Therefore a total of 39 subjects completed the study and were included in the pharmacokinetic and statistical analyses.

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

Treatment N=39	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	898 ± 369	--	79.9 ± 28.8	1.75 (1.0 - 4.0)	18.2 ±3.9
Reference	885 ± 348	--	83.9 ± 31.3	1.75 (1.0 - 4.0)	18.3 ± 4.5
***Ratio (90% CI)**	1.01 (0.97 - 1.04)	--	0.95 (0.90 - 1.00)	--	--
CV (%)	8.8	--	12.3	--	--

$AUC_{0-\infty}$ 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 levonorgestrel under fasted conditions.

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	62.5 ± 27.1	--	4.74 ± 1.95	1.25 (0.75 - 4.0)	55 ± 21
Reference	60.6 ± 26.0	--	5.05 ± 2.05	1.25 (0.75 - 4.0)	58 ± 46
***Ratio (90% CI)**	1.03 (0.97 - 1.09)	--	0.94 (0.87 - 1.01)	--	--
CV (%)	14.6	--	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
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} 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 levonorgestrel and ethinylestradiol under fasted conditions, it can be concluded that Zulima 150/30 micrograms and Microgynon 30 tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MAH did not reported the $AUC_{0-\infty}$ data as requested in the current guideline nor a justification was submitted for this omission. However, as the blood samples were taken over a period of 72 hours, this is

considered long enough to cover the whole absorption process. The mean C_{72h} concentrations were for ethinylestradiol 1.8 pg/ml (2% of the mean C_{max}) and for levonogestrel 0.4 ng/ml (8% of the mean C_{max}), respectively. Therefore the information regarding the $AUC_{0-\infty}$ is not informative and does not contribute to the assessment of bioequivalence. The omission is therefore considered acceptable.

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.

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 LNG and EE has been on the European market for decades. The safety profile of this combination can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC.
The MAH provided a Risk Management Plan (RMP), which includes the following major information:

Summary –Safety concerns

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

The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

Product information

SPC

During the procedure, updated SPCs were provided to comply with the CSP for ethinylestradiol and levonorgestrel containing products (agreed upon in procedure DK/H/PSUR/0054/001) and to harmonise the texts with the general SPC text for combined oral contraceptives agreed upon during the referral procedure for Yasminelle (NL/H/0701).

Readability test

The package leaflet has not been evaluated via a user consultation study. A bridging report was submitted with reference to the successfully user tested PL for a levonorgestrel/ethinylestradiol product with 7 placebo tablets. The text is nearly the same and the layout of the daughter PL is similar to the parent PL. Differences between the texts have been highlighted and discussed in the report. Since the differences do

not affect the key safety information, readability should not be affected and therefore no separate testing of the daughter PIL is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Zulima 150/30 micrograms, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Microgynon 30, 0.15 mg/0.03 mg, coated tablets. Microgynon 30 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 Zulima 150/30 micrograms, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 15 August 2013. Zulima 150/30 micrograms, film-coated tablets was authorised in the Netherlands on 24 October 2013.

The date for the first renewal will be: 15 August 2018.

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

Quality - medicinal product

- The MAH committed to validate the process at industrial scale. Once validated, the full-scale process validation results will be submitted for the authorities' approval.
- The MAH committed to submit three production batches of the product to stability testing. Testing at the same conditions (40ºC ± 2ºC/75%RH ± 5% and 25ºC ± 2ºC/60% ± 5%RH) as those used for the registration batches will be done.
- The MAH committed to add at least one production batch to the follow up stability programme.

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