CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Bryoronna 28 150/30 micrograms, film-coated tablets
Laboratorios León Farma S.A., Spain

desogestrel/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/2509/002/DC
Registration number in the Netherlands: RVG 110874

28 May 2013

Pharmacotherapeutic group:	progestogens and estrogens, fixed combinations
ATC code:	G03AA09
Route of administration:	oral
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of authorisation in NL:	19 March 2013
Concerned Member States:	Decentralised procedure with BE, ES, PL (withdrawn 150/20 micrograms product only)
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 Bryoronna 28 150/30 micrograms, film-coated tablets from Laboratorios León Farma S.A. The date of authorisation was on 19 March 2013 in the Netherlands.

The product is indicated for oral contraception.

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

In contrast the member states consider application NL/H/2509/001/DC regarding Geroldeme 28 150/20 micrograms film-coated tablets for the same indication, **not approvable** since "potential serious risks for public health" remain, which preclude a recommendation for marketing authorisation at the present time. Bioequivalence studies were not performed with this strength and similarity of the *in vitro* dissolution profiles was not demonstrated. Moreover, for the 150/20 µg strength the reference product is different from the reference product used in the bio-equivalence study. Therefore, a biowaiver could not be granted for the 150/20 micrograms product. The MAH decided to withdraw the application before finalisation of the decentralised procedure.

The product is a combination oral contraceptive. 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.
Direct measurements of plasma hormone levels indicate that LH and FSH levels are suppressed, a midcycle surge of LH is absent and endogenous steroid levels are diminished. While either component alone can be shown to exert these effects in certain situations, the combination synergistically decreases plasma gonadotropin levels and suppresses ovulation more consistently than either alone.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Marvelon tablets (NL License RVG 08859) which has been registered in the Netherlands by N.V. Organon since 29 May 1981. In addition, reference is made to Marvelon 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 Microdiol 0.03/0.15 mg tablets, registered in Spain. 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 substance
Desogestrel
The active substance desogestrel is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white, crystalline powder, which is practically insoluble in water. Desogestrel has six chiral centers, but does not exhibit polymorphism.

The CEP procedure is used for the desogestrel. 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 is tested in accordance with the Ph.Eur. monograph with additional tests on residual solvents, any other impurity and particle size distribution. Certificates of analysis of three batches have been provided, demonstrating compliance with the specification.

Stability of drug substance
A retest period of 3 years is applicable 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 Ph.Eur. It is a white to practically white crystals or powder, which is practically insoluble in water, freely soluble in ethanol and dissolves in dilute alkaline solutions. Ethinylestradiol has five chiral centers and exhibits polymorphism in the form of solvates/hydrates. The consistency and control of the anhydrate/hemi-hydrate manufactured was adequately discussed.

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 is tested in accordance with the Ph.Eur. monograph with additional tests on residual solvents, any other impurity and particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
A retest period of 5 years is applicable when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition
Bryoronna 28 150/30 micrograms contains 0.150 mg of desogestrel and 0.030 mg of ethinylestradiol and is a white, round film-coated tablet of 5.00 mm diameter.

The tablets are packed in blisters of aluminium push-thru foil and clear to slight opaque PVC/PVDC film. Each blister contains 28 film-coated tablets (21 active tablets plus 7 placebo tablets). The placebo tablets are green, round film-coated tablets of 5.00 mm diameter.

Bryoronna 28 150/20 micrograms contains 0.150 mg of desogestrel and 0.020 mg of ethinylestradiol and is a white, round film-coated tablet of 5.00 mm diameter and is also

The excipients in the active tablet are:
Tablet core - lactose monohydrate, maize starch, povidone K-30 (E1201), d-Alpha-tocoferol (E307), soybean oil, silica colloidal hydrated (E551), silica colloidal anhydrous (E551), stearic acid (E570)
Film-coating - hypomellose 2910 (E464), triacetin (E1518), polysorbate, titanium dioxide (E171).

The placebo tablets consist of:
Tablet core - lactose monohydrate, maize starch, povidone K-30 (E1201), silica colloidal anhydrous (E551), magnesium stearate (E572)
Film-coating - hypomellose 2910 (E464), riacetin (E1518), polysorbate, titanium dioxide (E171), FD&C Blue 2 Aluminium lake (E132), Yellow Iron Oxide (E172)

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. A direct compression process was chosen as the manufacturing process.
The dissolution method is based on USP test 2 and is justified over the BP method by comparative dissolution profiles and the discriminating nature of the dissolution method. The choice of container closure system is justified for the PVC/PVDC-Al blister.
The reference product used in the bioequivalence study is Microdiol®. Microdiol® is the name of the reference product in Spain which corresponds to Marvelon® in most European countries. The composition of innovator products is the same in most of the European countries, therefore, the innovator product used in the bioequivalence study is representative for the innovator products from all member states involved in this procedure.
The pharmaceutical development of the product has been adequately performed, but no biowaiver can be granted for the 150/20 micrograms strength as the reference products are based on different dossiers and because the similarity of the *in vitro* dissolution profiles of the 150/20 micrograms strength with the 150/30 micrograms strength biobatch has not satisfactorily been demonstrated. As was concluded in the clinical assessment, only the 150/30 micrograms strength can be accepted at this point. The necessity for inclusion of the antioxidant and the efficacy of the proposed levels have been shown. Although the inclusion of placebo tablets is not in line with the reference products, there is no objection from a quality point of view. The pharmaceutical development of the product was adequately performed.

Manufacturing process
The drug product is manufactured by a direct compression process. The active substances are pre-mixed separately before mixing. The premixes are then blended together and blend is compressed into tablet cores, coated and packed into blisters. The provided in-process controls are deemed acceptable.
The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques, but given the low concentration of active substance in the drug product, the manufacturing process can be considered as non-standard. Full-scale process validation results will be submitted by means of variation procedures.

Control of excipients
The excipients are tested in accordance with their respective Ph.Eur. monograph. The coating mixtures are controlled in-house. For vitamin E absorbed to silica specifications has been set for the silica as per Ph.Eur. monograph. The vitamin E consists of a mixture of RRR-alpha-tocopherol with soy bean oil. A specification has been set for this mixture in line with the USP monograph for vitamin E preparations and additional requirements as stated in the Food Chemical Codex (USA). These specifications are acceptable.

Quality control of drug product
The drug product specifications includes tests for appearance, identification, water content, hardness, dissolution, assay, related substances, uniformity of dosage units (content uniformity) and microbiological quality. The shelf-life specifications differ with respect to limits for assay and related substances.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches of each tablet strength, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the drug product has been provided on three pilot-scale batches, stored at 25°C/60% RH (up to 24 months), 30°C/65%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 accelerated conditions demonstrate that the drug product is sensitive to elevated temperatures. Out of specification values are observed for desogestrel assay after 6 months at accelerated conditions.
The 12 months of intermediate stability data demonstrate variation for assay, but no clear trends could be observed. Increases in impurities and decrease in d-Alpha-tocoferol were observed, but the results remain within limits. The results under long-term and intermediate storage conditions justify the proposed shelf-life of 24 months with the storage condition “Do not store above 30°C”. A photostability study has been performed in line with ICH topic Q1B. The results demonstrate that the drug product is photostable when packed in the proposed clear transparent PVC/PVDC-Al blisters. Therefore, the storage condition “Store in the original package in order to protect from light’ is also included.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A TSE declaration has been provided by the MAH for lactose monohydrate. It comes from milk of healthy animals collected under the same conditions as milk suitable for human consumption. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Marvelon, 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 ethinylestradiol or desogestrel 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

Ethinylestradiol or desogestrel is a 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 Bryoronna 28 150/30 micrograms (Laboratorios León Farma S.A., Spain) is compared with the pharmacokinetic profile of the reference product Microdiol® 0.03/0.15 mg tablets (Merck Sharp & Dohme de España, S.A., Spain).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of 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 60 healthy females of childbearing potential or pre-menopausal females with tubal ligation between 21 and 45 years of age. Each subject received a single dose (150/30 micrograms) of one of the 2 desogestrel/ethinylestradiol formulations. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.3, 0.7, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Bioequivalence will be based on the active metabolite 3-keto-desogestrel as it can reasonably be assumed that no measurable plasma concentrations of the parent compound desogestrel will be achieved in this study. Measurement of 3-keto-desogestrel is truncated at 72 hours as a result of its long half life.

The study design is acceptable. The sampling period and sampling scheme are adequate to properly estimate pharmacokinetic parameters. Desogestrel is rapidly absorbed and completely converted into 3-keto-desogestrel. Measurement of the metabolite 3-keto-desogestrel is justified by the achievement of non measurable plasma concentrations of the parent compound desogestrel in this study.

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
Fifty-eight subjects completed the study and were included in pharmacokinetic and statistical analysis. The two drop-outs were a withdrawal during the first dosing period due to vomiting and 1 subject who withdrew due to personal reasons before the start of the second period.

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

Treatment N=58	**AUC_{0-t}** pg/ml/h	**$AUC_{0-\infty}$** pg/ml/h	**C_{max}** pg/ml	**t_{max}** h
Test	710 ± 249	772 ± 356	69 ± 21	1.5 (1.0-2.5)
Reference	711 ± 215	754 ± 220	74 ± 22	1.5 (1.0-2.25)
***Ratio (90% CI)**	0.99 (0.95-1.03)	1.00 (0.95-1.05)	0.93 (0.89-0.96)	
$AUC_{0-\infty}$ 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 3-keto-desogestrel under fasted conditions.

Treatment N=58	**AUC_{0-t}** pg/ml/h	**$AUC_{0-\infty}$** pg/ml/h	**C_{max}** pg/ml	**t_{max}** h
Test	9764 ± 3848	--	1340 ± 391	1.25 (0.7-3.0)
Reference	10229 ± 4526	--	1409 ± 490	1.5 (1.0-4.0)
***Ratio (90% CI)**	0.97 (0.94-0.99)	--	0.99 (0.91-1.04)	

$AUC_{0-\infty}$	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 ethinylestradiol and 3-keto-desogestrel under fasted conditions, it can be concluded that Bryoronna 28 150/30 micrograms and Microdiol® 0.03/0.15 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Desogestrel/ethinylestradiol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of desogestrel and ethinylestradiol. 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).

Biowaiver application for the lower strength

The results of the bioequivalence study with the 150 µg/30 µg formulation cannot be extrapolated to the other strength 150 µg/20 µg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The applicant requested a waiver for an *in vivo* bioequivalence study with the other strength: the 150 µg/ 20 µg desogestrel/ethinylestradiol tablet. However, this is not acceptable as the lower strength is based on another originator product. This originator product is Mercilon 150 µg/20 µg tablets, whereas the innovator product for the higher strength (150 µg/30 µg) is Marvelon. As the bioequivalence study is performed with only the highest strength, the comparability and dose proportionality of the separately registered originator products cannot be guaranteed. Moreover, similarity of the *in vitro* dissolution profiles of the 150/20 micrograms tablet and the 150/30 micrograms biobatch has not been satisfactorily demonstrated. A biowaiver for a bioequivalence study with the lower strength cannot be granted. Therefore, the applicant chose to officially withdraw the applicaiton for the lower strength before finalisation of the procedure.

Risk management plan

Desogestrel/ethinylestradiol was first approved in 1981, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of desogestrel/ethinylestradiol 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. 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 Marvelon.

Readability test

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. In both rounds of testing, all subjects were able to locate the requested information and provided the correct response. Therefore, no changes to the PL were made. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Bryoronna 28 150/30 micrograms, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Marvelon tablets. Marvelon is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence for the 150/30 micrograms tablet has been shown to be in compliance with the requirements of European guidance documents. The application for Geroldeme 28 150/20 micrograms was withdrawn, as no biowaiver could be granted for this strength.

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.

In the Board meeting of 5 December 2012, the vitamin E specification, which was set in line with the USP monograph for vitamin E preparations, was discussed. The Board agreed that this specification is appropriate to control the quality.

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 Bryoronna 28 150/30 micrograms, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 5 December 2012. Bryoronna 28 150/30 micrograms, film-coated tablets was authorised in the Netherlands on 19 March 2013.

The date for the first renewal will be: 5 December 2017.

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

Quality - medicinal product

- The MAH committed to submit data on the batch scale-up by means of the appropriate variation procedure. Batch scale up validation will include comparative dissolution profile testing as well.
- The MAH committed to provide updated stability data when available.

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
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
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