CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ethinylestradiol/Desogestrel Mylan 0.02/0.15 mg and 0.03/0.15 mg tablets
Mylan B.V., the Netherlands

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/2102/001-002/DC
Registration number in the Netherlands: RVG 108170-108171

13 August 2012

Pharmacotherapeutic group:	hormonal contraceptives for systemic use; progestogens and estrogens, fixed combinations; desogestrel and estrogen
ATC code:	G03AA09
Route of administration:	oral
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of authorisation in NL:	2 August 2012
Concerned Member States:	Decentralised procedure with BE, DE, DK, ES, FI, HU, IT, NO, PL, PT, SE and UK
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 Ethinylestradiol/Desogestrel Mylan 0.02/0.15 mg and 0.03/0.15 mg tablets from Mylan B.V. The date of authorisation was on 2 August 2012 in the Netherlands. The product is indicated for oral contraception.

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

Desogestrel/Ethinylestradiol tablet 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 products Mercilon (NL license RVG 11508) and Marvelon (NL license RVG 08859) marketed by N.V. Organon. For the tablets containing 150 µg desogestrel and 20 µg ethinylestradiol, Mercilon tablets are used as reference product. For the tablets containing 150 µg desogestrel and 30 µg ethinylestradiol, Marvelon tablets are used as reference product. The reference products have been authorised in the Netherlands since 19 November 1987 and 29 May 1981 respectively, by means of a national procedure. In addition, reference is made to Mercilon and 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 two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Mercilon and Marvelon registered in the Netherlands. 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 medicinal product.

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

Desogestrel
One active substance is desogestrel, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Desogestrel is a white to practically white crystalline powder. The active substance is practically insoluble in water, slightly soluble in ethanol and ethyl acetate, and sparingly soluble in n-hexane.
Desogestrel has six chiral centers and exhibits polymorphism. Because the drug substance is dissolved before the manufacture of the drug product, information on polymorphism and particle size distribution is not considered necessary.

The CEP procedure is used for 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 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 is tested in accordance with the Ph.Eur. monograph with additional tests on residual solvents. Batch analytical data have been provided.

Stability of drug substance
Stability data on the active substance have been provided for 4 batches stored at 40°C/75% RH (6 months) and for 6 batches stored at 25°C/60% RH (five batches for 60 months, one batch for 36 months). The retest period has been set at 60 months at 15-25 ºC in its original, closed and undamaged container. It is stated that each year one production scaled batch will be put into a stability study using the ICH long term storage condition.

Ethinylestradiol
The other active substance, ethinylestradiol, is also an established active substance, described in the Ph.Eur. The active substance is practically insoluble in water, freely soluble in ethanol and dissolves in dilute alkaline solutions. Ethinylestradiol has five chiral centers, but does not exhibit polymorphism.

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 suitablity 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 specification of ethinylestradiol is fully in line with the currently valid Ph.Eur. monograph 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 proposed 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.*

Medicinal Product

Composition
The tablets are white to off-white, round, biconvex and uncoated, containing 20 µg or 30 µg ethinylestradiol and 150 µg desogestrel. The tablets are debossed with either '141' (150 µg/20 µg) or '142' (150 µg/30 µg) on one side and plain on the other side.
The excipients are: all-*rac*-alpha-tocopherol, potato starch, povidone (E1201), stearic acid (E570), silica, colloidal anhydrous (E551) and lactose anhydrous. The two formulations contained the same amount of excipients.

The drug product is packed in clear transparent PVC/PVDC-Al blisters in tri-laminated pouch (with or without a molecular sieve). The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The pharmaceutical development of the product has been adequately described. The choice of excipients is justified and their functions explained. The development of the clinical batches is discussed and comparative dissolution profiles at different pH levels are provided. The equivalence of the innovator product with the innovator products from all member states involved is demonstrated. Essential similarity has been demonstrated.

Manufacturing process
The manufacturing process is considered to be a non-standard process due to the low content of active substances. The process consists of several mixing steps, followed by granulation, drying and compression. The provided in-process controls are acceptable. The manufacturing process has been adequately validated according to relevant European guidelines.

Excipients
All excipients are tested in accordance with their respective Ph.Eur. monograph.

Quality control of drug product
The drug product specifications includes tests for appearance, identification, identification and assay of vitamin E, dissolution, assay, related substances, uniformity of dosage units (content uniformity), residual solvents, microbiological requirements and water content. The shelf-life specifications are the same as the release specification, with the exception of the limit for assay, dissolution, related substances and vitamin E content. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot scaled batches of each tablet strength, demonstrating compliance with the release specifications.

Stability of drug product
A photo stability study is performed and sensitivity to light was shown. Stability data on the active drug product has been provided on three pilot scale batches of each tablet strength, stored at 25°C/60% RH (up to 18 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 clear transparent PVC/PVDC-Al blisters in tri-laminated pouches; sub batches of each batch for a packaging with molecular sieve and without the molecular sieve.
The accelerated conditions demonstrate that the drug product is sensitive to elevated temperatures. Under all conditions, a decrease in assay and dissolution and an increase in impurities are observed.
A mass imbalance of ethinylestradiol during stability was explained. As demonstrated by accelerated studies the product is light sensitive and moisture sensitive. The granted shelf life, packaging material and

storage conditions are: 24 months in PVC/PVDC-Al blisters with or without molecular sieve; Do not store above 25°C, store in the original package in order to protect from moisture and light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate is of vegetable origin and lactose anhydrous complies with the Note for Guidance EMEA/410/01 rev.2, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Mercilon/Marvelon, 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 desogestrel 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

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

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Ethinylestradiol/Desogestrel Mylan 0.02/0.15 mg and 0.03/0.15 mg tablets (Mylan B.V.) are compared with the pharmacokinetic profile of respectively the reference products Mercilon (study I) or Marvelon (study II) by N.V. Organon.

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.

Study I – Desogestrel/Ethinylestradiol 0.15/0.02 mg tablets compared with Mercilon

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy female subjects of child bearing potential. Each subject received a single dose (2 x 0.15 mg/0.02 mg) of one of the 2 desogestrel/ethinylestradiol formulations. The tablets were orally administered with 240 ml water after an overnight fasting of at least 10 hours. There were 2 dosing periods, separated by a washout period of 28 days.
Blood samples were collected in each period at 0.0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours after administration of each dose. The plasma samples were analysed for 3- ketodesogestrel (etonogestrel) and ethinylestradiol. The measurement of the active metabolite 3-ketodesogrestrel is agreed as desogestrel is rapidly absorbed and completely converted into 3-keto-desogestrel.

Analytical/statistical methods
The analytical methods for the determination of plasma levels of 3-ketodesogestrel and of ethinylestradiol were validated and considered adequate. The analytical method is adequately validated and 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

The plasma concentration data of 31 subjects who completed both study periods were included in pharmacokinetic and statistical analysis. In addition, study samples of one subject (withdrawn on medical grounds) was analysed on basis of protocol requirement (safety basis).
Three subjects dropped out, one subject discontinued on the grounds of protocol deviation in period I, one subject discontinued on check-in day of period II on medical grounds (fever at check in) and one subject discontinued from the study as she did not report for the period II check-in. The first mentioned subject did not report for three consecutive ambulatory samples in period I, furthermore this subject had a positive pregnancy test during safety follow up.
Pre-dose concentrations of 3-ketodesogestrel were found in period II in one subject, with a pre-dose plasma concentration of 3-ketodesogestrel (previous to administration of the test tablet) greater than 5% C_{max} value. Pre-dose concentrations of ethinylestradiol were found as well, in period I. The pre-dose plasma concentration of ethinylestradiol in one subject (previous to administration of the test tablet) was greater than 5% C_{max} value. Re-evaluation of the selection of study subjectsm, the in- and exclusion criteria, the check-in procedure and a compliance check did not reveal an obvious reason for the pre-dose concentrations in study I. It was decided to exclude the two subjects from the pharmacokinetic and statistical analysis due to the high pre-dose concentrations. This is considered acceptable as the protocol is acceptable and the MAH showed strict adherence to the protocol.
A pharmacokinetic evaluation without the data of the two subjects for both analytes was performed. After excluding data of these subjects, 90% confidence interval is well within the acceptance range for all three primary pharmacokinetic parameters (see table 1 and 2).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 3-ketodesogestrel under fasted conditions.

Treatment N=29	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	53199.824	71881.247	4392.796	--	--
Reference	54194.783	73909.545	4604.031	--	--
***Ratio (90% CI)**	0.98 (0.92-1.04)	0.97 (0.89-1.06)	0.95 (0.87 -1.05)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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=29	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	868.110	952.282	97.030	--	--
Reference	863.422	932.832	92.481	--	--
***Ratio (90% CI)**	1.01 (0.95-1.07)	1.02 (0.97-1.08)	1.05 (0.99-1.12)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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 desogestrel and ethinylestradiol under fasted conditions, it can be concluded that Ethinylestradiol/Desogestrel Mylan 0.02/0.15 mg tablets and the Mercilon are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety

Safety was assessed from the screening period to the end of the study. It was assessed through clinical examinations, vital signs assessment, ECG, X-ray chest, pelvic examinations, PAP smear test, clinical laboratory parameters (e.g. haematology, biochemistry, serum electrolytes, urine analysis and immunology) and subjective symptomatology, and by recording and monitoring of adverse events. Safety was adequately monitored.

A total of 16 adverse events were reported during the course of the study in 9 subjects. According to the MAH, 6 events were possibly related to the study medication (4 for the test tablet and 2 for the reference tablet. All adverse events were mild in nature and resolved. One subject who was discontinued in period-I, found to have raised β-HCG level in the post study safety assessment (during follow up, pregnancy was confirmed). There was no serious or significant adverse event reported during the course of the study.

Study II – Desogestrel/Ethinylestradiol 0.15 mg/ 0.03 mg tablets compared with Marvelon

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy female subjects of child bearing potential. Each subject received a single dose (2 x 0.15 mg/0.03 mg) of one of the 2 desogestrel/ethinylestradiol formulations. The tablets were orally administered with 240 ml water after an overnight fasting of at least 10 hours. There were 2 dosing periods, separated by a washout period of 29 days.

Blood samples were collected in each period at 0.0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours after administration of each dose. The plasma samples were analysed for 3- ketodesogestrel (etonogestrel) and ethinylestradiol.

Analytical/statistical methods

The analytical methods for the determination of plasma levels of 3-ketodesogestrel and of ethinylestradiol were validated and considered adequate. The analytical method is adequately validated and 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

The plasma concentration data of 24 subjects who completed both study periods were included in pharmacokinetic and statistical analysis. Nine subjects discontinued from the study on medical grounds, as they vomited after dosing in period I or period II. One subject withdrew her consent for further participation in the study and did not report for check-in of period II. The number of drop out subjects is high. The reasons for discontinuation were given for all subjects and were according to protocol; therefore the high number of drop out subjects was accepted.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 3-ketodesogestrel under fasted conditions.

Treatment N=24	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	39783 ±15176	54748 ± 21563	2978 ±1253	1.5 (1.0-4.0)	57 ±22
Reference	37193 ±15674	50558 ± 23684	3243 ±1395	2.0 (1.0-3.5)	56 ± 21
***Ratio (90% CI)**	1.09 (0.99- 1.20)	1.10 (0.99-1.22)	0.95 (0.83-1.09)	-	-
CV (%)	20	21	27	-	-

$AUC_{0-\infty}$ 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=24	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1849 ±650	1906±665	153 ±47	1.5 (1.0-3.5)	17 ± 3
Reference	1896 ±625	1946 ±637	166 ±49	1.5 (1.0-2.5)	16 ±3
***Ratio (90% CI)**	0.97 (0.95- 0.99)	0.97 (0.95- 1.00)	0.91 (0.88- 0.96)	-	-
CV (%)	5	5	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*

The mean extrapolated AUC was higher than 20% for both analytes, but as the sampling time was sufficiently long (96 hours) and covered the absorption phase, this is not considered a problem. No pre-dose levels were detected, not in the first and not in the second period.

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 (active substance) under fasted conditions, it can be concluded that Ethinylestradiol/Desogestrel Mylan 0.03/0.15 mg tablets and Marvelon are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
During the course of study, safety parameters assessed were vital signs, physical examination, medical history, clinical laboratory safety tests (hematology, biochemistry, immunology, urine analysis, serum β-HCG, chest X-ray, ECG, completed obstetrics and gynecological examination, breast examination and transvaginal ultrasonography) at baseline. Laboratory parameters of haematology, biochemistry and serum β-HCG tests were reassessed at 96 hours post dose of the last study period. The data on adverse events were collected and tabulated. Safety was adequately monitored.
A total of 28 adverse events were reported during the entire study. According to the MAH, 11 adverse events were considered related to the oral administration of the test product. Seventeen adverse events were considered related to the oral administration of reference product. All these events were considered mild. None of the subjects experienced serious adverse events.

Food interaction
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).

Risk management plan
The combination of desogestrel and ethinylestradiol was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of desogestrel and 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 the general SPC text for combined oral contraceptives that has been agreed upon during the referral procedure for Yasminelle, with exception of the text that is specific for the active substance drospirenone, a component of Yasminelle but not of this product, and with exception of the product specific sections.

Readability test
The package leaflet (PIL) 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 evaluation report of the test is of an acceptable quality. The criteria for the user test have been met.
The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. Inclusion and exclusion criteria of the test persons were specified in the protocol. The test was performed in English. Educational levels correspond with the inclusion criteria set in the protocol. The test was performed by face-to-face interviews. Questions were designed to determine whether users can identify key information that is necessary for appropriate use.

There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. The test included 20 questions related to the content of the PIL. Three questions were related to the structure/appearance of the PIL.
Participants were interviewed individually by one interviewer. The responses were written down by hand/recorded by voice recorder. A satisfactory outcome was achieved when 90% of the participants were able to find information and when 90% was able to show that they could understand the information and act appropriately.
The MAH indicated that all questions met the criteria. In round 1, 100% of the time the correct section was located to answer the question, although some participants did only find the information ‘with great difficulty”. Each question was correctly answered 100% of the time. In the second round 100% of the participants were able to locate the section and again some participants did only find the information ‘with great difficulty”. All participants were able to answer the questions. Therefore no further changes were considered to be required. The user test is considered acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ethinylestradiol/Desogestrel Mylan 0.02/0.15 mg and 0.03/0.15 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Mercilon/Marvelon. Mercilon and Marvelon are 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 SPC, package leaflet and labelling are in the agreed templates and are in agreement with other desogestrel and ethinylestradiol containing products.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ethinylestradiol/Desogestrel Mylan 0.02/0.15 mg and 0.03/0.15 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 22 November 2011. Ethinylestradiol/Desogestrel Mylan 0.02/0.15 mg and 0.03/0.15 mg tablets are authorised in the Netherlands on 2 August 2012.

The first PSUR must be submitted with a data lock point of October 2013.
The PSUR submission cycle is 3-yearly.

The date for the first renewal will be: 30 June 2014 (8 months after the data lock point).

Quality - medicinal product

- The MAH committed to review the release and end of shelf-life specification of the impurities when more stability data becomes available and revise the limits accordingly.
- The MAH committed to submit data of the vitamin E content 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