CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ethinylestradiol/Desogestrel 0.02 mg/0.15 mg and 0.03 mg/0.15 mg Teva, tablets Teva Nederland 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/2673/001-002/DC
Registration number in the Netherlands: RVG 112197, 112201

10 July 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:	6 June 2013
Concerned Member States:	Decentralised procedure for 0.02/0.15 mg with AT, DK, EE, FI, HU, IS, LT, LV, RO, for 0.03/0.15 mg with BE, DK, EE, HU, LT, LV, RO
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 0.02 mg/0.15 mg and 0.03 mg/0.15 mg Teva, tablets from Teva Nederland B.V. The date of authorisation was on 6 June 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 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 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. 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 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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification is in line with Ph.Eur. and the additional parameters as mentioned on the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification has been provided.

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.

** 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 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. Two polymorphic forms of the drug substance are described, having very distinctive melting points, the form used is sufficiently described and manufactured consistently.

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 specification of ethinylestradiol is fully in line with the currently valid Ph.Eur. monograph and the additional tests laid down in the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided.

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
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 contain 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) of 21 tablets per calendar blister strip and available in packs containing 1x21, 3x21, 6x21 or 13x21 tablets. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. During development composition and process parameters were optimised until the final formulation was obtained. No similarity of dissolution profiles between test and reference product for the desogestrel component is demonstrated for the 150/20 mg strength in the 4.5 pH acetate and the pH 6.8 phosphate buffer solutions. However, as bioequivalence is demonstrated for both tablet strengths this is acceptable.

Manufacturing process
The manufacturing process involves the following steps: mixing of active substance with the dry excipients, mixing with the rest of the excipients creating a solution, granulation, drying and sifting. The blend is compressed into tablet cores, coated and packed into blisters.
The manufacturing process has been adequately validated, and the parameters tested complied with the pre-set limits. The proposed production batches are adequately validated.

Control of excipients
The excipient used and their quantities, are common for this type of formulation. Analytical procedures for all the excipients are performed as per requirement specified in the Ph.Eur.

Quality control of drug product
The product specification includes tests for appearance, identification of the active substances and vitamin E, water content, dissolution, content uniformity, assay of the active substances and vitamin E, related substances, residual solvents, and microbial contamination. The specifications at release and end-of-shelf-life are identical for all the test procedures, except for the limits for dissolution and assay of ethinylestradiol, assay of vitamin E and related substances. The analytical methods have been adequately described and validated. The provided data on three commercial-scale batches per strength show compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for six commercial-scale batches (three per strength) stored at 25°C/60%RH for 24 months) and 40°C/75%RH for 24 weeks. The batches were stored in the proposed packaging material. The conditions used in the stability studies are according to the ICH stability guideline, stability data covering the proposed shelf life is available. Moreover, stability data was provided

for six scale-up batches (three batches per strength), covering 6 months long-term and accelerated conditions for the 30/150 microgram strength, and three months for the 20/150 microgram strength. The batches were stored in the trilaminated aluminium pouches without molecular sieve.
Furthermore, an in-use study was performed. This was performed since the stability results indicate that the drug product is influenced by its packaging material (differences were observed in terms of water content and impurities, between the product packed with molecular sieve and without). No significant changes were observed in the 30 days in-use stability study. In addition, a photostability study was performed, demonstrating that the product is light sensitive.
Based on the available data, a shelf life of 24 months is acceptable, with the following storage condition: "This medicinal product does not require any special temperature storage conditions. 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. 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 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. 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 two bioequivalence studies in which the pharmacokinetic profile of the test products Desogestrel/Ethinylestradiol 0.02 mg/0.15 mg and 0.03 mg/0.15 mg Teva tablets (Teva Nederland B.V., the Netherlands) are compared with the pharmacokinetic profile of respectively the reference products Mercilon (study I) and 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.

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.

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 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. The measurement of the active metabolite 3-ketodesogrestrel is agreed as desogestrel is rapidly absorbed and completely converted into 3-keto-desogestrel.

The design of the study is acceptable; the sampling period was long enough, the sampling scheme adequate to estimate the pharmacokinetic parameters. The washout period of 29 days is long enough to minimize the possibility of a carry-over effect.

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 concentration of 3-ketodesogestrel was found in period II in one subject, with a pre-dose plasma concentration (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 in another subject with a pre-dose plasma concentration (previous to administration of the test tablet) greater than 5% C_{max} value. Re-evaluation of the selection of study subjects, 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=30	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	55045 ± 16642	73744 ± 21683	4703 ± 1751	1.5 (1.0-2.5)	58 ± 39
Reference	57434 ± 18628	78100 ± 28858	5124 ± 2321	2.0 (1.0- 3.5)	60 ± 51
***Ratio (90% CI)**	0.96 (0.90-1.03)	0.96 (0.87-1.04)	0.93 (0.84-1.03)	--	--
CV (%)	19	26	30	--	--

$AUC_{0-\infty}$	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=30	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	935 ± 391	1021 ± 406	101 ± 34	1.5	16 ± 6
Reference	938 ± 392	1009 ± 407	96 ± 32	1.5	14 ± 5
***Ratio (90% CI)**	1.01 (0.95-1.07)	1.03 (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 Desogestrel/Ethinylestradiol 0.15 mg/0.2 mg Teva and Mercilon tablets 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.

The design of the study is acceptable; the sampling period was long enough, the sampling scheme adequate to estimate the pharmacokinetic parameters. The washout period of 29 days is long enough to minimize the possibility of a carry-over effect.

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 3. 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 4. 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 desogestrel and ethinylestradiol under fasted conditions, it can be concluded that Desogestrel/Ethinylestradiol 0.15/0.03 microgram and Marvelon tablets 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.
The agreed CSP text of an Art.45 Paediatric Worksharing for Desogestrel/Ethinylestradiol (CZ/W/006/pdWS/001) has been implemented.

Readability test

The package leaflet has not been evaluated via a user consultation study. The MAH submitted a bridging statement to declare that the package leaflet for Desogestrel 150 microgram and Ethinylestradiol 20 microgram tablets is identical to the previously tested package leaflet for Desogestrel 150 microgram and Ethinylestradiol 30 microgram tablets with the sole difference between the two leaflets being the strength of one of the active substances: ethinylestradiol.
In the bridging statement the MAH declares that, as the information regarding the strength is the only differing aspect between the PILs, the result of the Readability Test for Desogestrel 150 microgram and Ethinylestradiol 30 microgram Tablets also applies to the PIL for Desogestrel 150 microgram and Ethinylestradiol 20 microgram Tablets.
The technical specifications of both leaflets are identical. Techniques to improve readability of the leaflet such as bullet-point lists and bold font were applied in similar ways to both PILs.
Both PILs were written in English according to the QRD template. Identical sentences were used for the information presented in both PILs. The member states accepted the bridging report. Separate user testing of the proposed PIL is not necessary.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ethinylestradiol/Desogestrel 0.02 mg/0.15 mg and 0.03 mg/0.15 mg Teva 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ethinylestradiol/Desogestrel 0.02 mg/0.15 mg and 0.03 mg/0.15 mg Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 May 2013. Ethinylestradiol/Desogestrel 0.02 mg/0.15 mg and 0.03 mg/0.15 mg Teva, tablets were authorised in the Netherlands on 6 June 2013.

The date for the first renewal will be: 1 May 2018.

PSUR submission is required for ethinylestradiol/desogestrel generics, with a 5-year cycle. The next data lock point is 30 September 2015.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to confirm the expiry date with real-time data. One production batch each year will be placed on stability and tested at long term conditions (25°C ± 2°C/60% RH ± 5%).

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
CSP	Core Safety Profile
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