CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Bellverene 28 0.02 mg/3 mg film-coated tablets
Bellverene 28 CF 0.03 mg/3 mg film-coated tablets
ELC-Group, momaja s.r.o, Czech Republic

ethinylestradiol/drospirenone

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/2632/001-002/DC
Registration number in the Netherlands: RVG 111660-111661

3 October 2013

Pharmacotherapeutic group:	progestogens and estrogens, fixed combinations
ATC code:	G03AA12
Route of administration:	oral
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of authorisation in NL:	1 August 2013
Concerned Member States:	Decentralised procedure with: 0.02 mg/3 mg - FR 0.03 mg/3 mg - SE
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 Bellverene 28 0.02 mg/3 mg and 0.03 mg/3 mg film-coated tablets from ELC-Group, momaja s.r.o. The date of authorisation was on 1 August 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 contraceptive effect of this drospirenone/ethinylestradiol combination is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the endometrium.
In a therapeutic dosage, the synthetic progestagen drospirenone also possesses antiandrogenic and mild antimineralocorticoid properties. It has no estrogenic, glucocorticoid and antiglucocorticoid activity. There are indications from clinical studies that the mild antimineralocorticoid properties of drospirenone/ ethinylestradiol result in a mild antimineralocorticoid effect.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Yasminelle 28, film-coated tablets 0.02/3 mg (NL/H/0704/001/MR, registered since 17 November 2005) and Yasmin 28, film-coated tablets 0.03/3 mg (NL/H/0217/001/MR, registered since 7 April 2000).

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 which are registered in France under the names Jasminelle, 3.0 mg/0.02 mg and Jasmine 3.0 mg/0.03 mg film-coated tablets. 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
Ethinylestradiol
The active substance ethinylestradiol is an established active substance, described in the European Pharmacopoeia (Ph.Eur.*). It is a white or slightly yellowish-white, slightly hygroscopic crystalline powder, which is practically insoluble in water and freely soluble in alcohol. It dissolves in dilute alkaline solutions. Ethinylestradiol exhibits only one not solvated polymorphic form.

CEP
The CEP procedure is used for one supplier of 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 the Ph.Eur. and the CEP. An additional test for one residual solvent is included. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data have been provided.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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.*

ASMF
The Active Substance Master File (ASMF) procedure is used for the second manufacturer of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The drug substance is manufactured by a one step synthesis. Following synthesis, the drug substance is purified and micronised. Sufficient information has been provided on the manufacturing process.

Quality control of drug substance

The drug substance specification is based on the Ph.Eur. monograph of ethinylestradiol with additional tests for residual solvents and particle size. In general, the specification is acceptable in view of the route of synthesis and the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches, analysed in accordance with the current monograph for ethinylestradiol and for three historical batches. The batches were stored at the long-term conditions 25ºC/60% RH (9 months for the current batches and 60 months for the historical batches) and at the accelerated conditions 40ºC/75% RH (6 months). A slight increase in related substances was observed. No other changes in stability indicating parameters were observed. All stability data reported comply with the proposed specifications. The proposed re-test period of two years is acceptable.

Drospirenone
The active substance drospirenone is an established active substance, described in the Ph.Eur. It is a white or almost white powder. Water solubility is 10.9 mg/l. Drospirenone does not show polymorphic forms.

The CEP procedure is used for this active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification is based on the Ph.Eur. monograph of drospirenone with additional tests for residual solvents. The specifications are acceptable in view of the route of synthesis and the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 36 months when stored in a double polyethylene bag into a polyethylene drum. No special storage conditions are required.

Medicinal Product

Composition
The medicinal products consist of blisters filled with 21 active tablets and 7 placebo tablets. Bellverene 28 0.02 mg/3 mg are round, pink film-coated tablets. Bellverene 28 0.03 mg/3 mg are round, yellow film-coated tablets. The placebo tablets are white, film-coated tablets without any active substance.

The pack is a clear to slightly opaque transparent PVC/PVDC-Al blister.

The excipients are:
0.02/3 mg
Tablet core - lactose monohydrate, pregelatinised starch (maize), povidone (E1201), sodium croscarmellose, polysorbate 80 (E433), magnesium stearate (E470b).
Coating - poly (vinyl alcohol), titanium dioxide (E171), macrogol, talc (E553b), yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172).

0.03/3 mg
Tablet core - lactose monohydrate, maize starch, pregelatinised starch (maize), crospovidone type A, crospovidone type B, povidone (E1201), polysorbate 80 (E433), magnesium stearate (E470b)
Coating - poly (vinyl alcohol), titanium dioxide (E171), macrogol, talc (E553b), yellow iron oxide (E172).

The placebo tablets contain lactose anhydrous, povidone K30, magnesium stearate and Opadry® II White (consisting of polivinyl alcohol, titanium dioxide, macrogol 3350 and talc).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The product development objective was to develop film-coated tablets that would be bioequivalent to the medicinal products Yasminelle® and Yasmin®, having the same qualitative and quantitative composition in drug substances per tablet and the same pharmaceutical form.
Development of the drospirenone 3 mg/ethinylestradiol 0.03 mg was simultaneous to that of the drospirenone 3 mg/ethinylestradiol 0.02 mg. Therefore, a common development strategy was followed for both formulations. The formulation with lower concentration of ethinylestradiol (*i.e.* 0.02 mg) was selected for testing. A water based wet granulation process was tried and experimental batches were tested and dissolution profiles were compared to the dissolution profile of the reference product.
Dissolution profiles at three different pH values were determined for test and reference batches used in the bioequivalence studies.
Additionally, a comparison of three industrial validation batches against the bioequivalence pilot batch and both reference products was performed. It was shown that all profiles are comparable. Sufficient in-vitro data have been presented.
A compatibility study was performed to describe potential interactions between the individual excipients and the active drug substances.
The container closure system (PVC-PVdC/aluminium blisters) is usual for this type of dosage form.

Manufacturing process
The drug product is manufactured by wet granulation. The process consists of blending, mixing, granulation, drying, milling, tablet compression and coating. The in-process controls for the manufacturing process of the active tablets are acceptable. The manufacturing process has been adequately validated according to relevant European Guidelines. For the placebo tablets, a direct compression method has been described. Adequate information on in-process controls has been provided. No process validation is required for the placebo tablets.

Control of excipients
All excipients are tested in accordance with their respective Ph.Eur. monograph, except for Opadry® II Pink, Opadry® II Yellow and Opadry® II White, which are tested according to in-house procedures. The specifications are acceptable.

Quality control of drug product
The active drug product specification includes tests for appearance, identification (release only), dissolution, assay, related substances, content uniformity (release only), residual solvents (release only) and microbial control. For appearance, dissolution, drospirenone assay and related substances and microbial control, the shelf-life specifications are the same as the release specifications. For assay of ethinylestradiol, the shelf-life specification is wider than the release specification, which is supported by stability data.
The placebo drug product specification includes tests for appearance, average weight, disintegration time and microbial control. The shelf-life specifications are the same as the release specifications.
The analytical methods have been adequately described and validated. The HPLC methods for assay and related substances are considered to be stability indicating.
Batch analytical data for two pilot batches and three industrial batches of each of the strengths of the drug product have been provided, as well as data for one pilot batch of the placebo tablets, demonstrating compliance with the release specifications.

Stability of drug product

Stability data on the placebo tablets have been provided for one pilot-scale batch, stored at 25°C/60% (36 months) and 40ºC/75% RH (6 months). The parameters appearance, disintegration time and microbial control remained within specifications. In view of the stability data presented, a shelf-life of 36 months for the placebo tablets is acceptable.
Stability data on the active drug product have been provided on two pilot-scale and three commercial-scale batches of each strength. The batches were stored at 25°C/60% RH (36 months for the pilot-scale and 12 months for the commercial-scale batches) 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 PVC/PVdC-Al blisters.
A photostability study in compliance with the NfG on Photostability Testing has been performed, which shows that the product is not sensitive to light. In view of the provided stability data, the claimed shelf-life of 36 months and the proposed storage conditions “Store below 30ºC” were granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE declarations have been provided for lactose monohydrate and lactose anhydrous, as they are of animal origin.

II.2 Non-clinical aspects

These products are generic formulations of Yasmin 28 and Yasminelle 28, which are 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 drospirenone 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

Drospirenone 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 Bellverene 28 0.02 mg/3 mg and Bellverene 28 0.03 mg/3 mg (ELC-Group, momaja s.r.o, Czech Republic) is compared with the pharmacokinetic profile of the reference products Jasminelle 3.0 mg/0.02 mg and Jasmine 3.0 mg/0.03 mg film-coated tablets (Schering S.A.S, France).

The choice of the reference product
The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – 3 mg/0.02 mg strength

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy females of childbearing potential, aged 20-43 years old. Each subject received a single dose of three tablets (3 x 3 mg/0.02 mg) of one of the 2 drospirenone/ethinylestradiol formulations. The tablets were orally administered with 240 ml water after a fasting period of at least 10 hours. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120 hours after administration of the products.

The design is acceptable for this kind of application, the wash-out of 28 days is sufficient and the sampling period long enough. Furthermore, the sampling scheme is adequate to estimate pharmacokinetic parameters. The administration of 3 tablets was considered necessary to achieve measurable plasma ethinylestradiol levels and justified by dose proportionality of drospirenone (1–10 mg) and Ethinylestradiol (20–60 µg). This is acceptable.

Results
Two subjects withdrew and did not show up for the second period. Therefore a number of 32 subjects completed the study. However, one subject was excluded from the analysis since pre-dose concentrations of >5% of C_{max} were observed in both periods for both compounds. Statistical analysis was performed with 31 subjects.

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

Treatment N=31	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1.3 ± 0.3	1.4 ± 0.4	85 ± 15	1.75	32.7
Reference	1.3 ± 0.3	1.4 ± 0.4	85 ± 17	1.75	31.9
***Ratio (90% CI)**	1.00 (0.97-1.02)	1.00 (0.98-1.02)	1.01 (0.94-1.07)	--	--
CV (%)	5.1	5.1	14.9	--	--

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ethinylestradiol under fasted conditions.

Treatment N=31	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1.4 ± 0.3	1.6 ± 0.3	142 ± 29	1.75	32.7
Reference	1.5 ± 0.3	1.7 ± 0.3	147 ± 29	1.75	31.9
***Ratio (90% CI)**	0.95 (0.90-0.99)	0.95 (0.90-0.99)	0.96 (0.91-1.02)	--	--

CV (%)	11.1	10.5	13.8	--	--

$AUC_{0-\infty}$ 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 drospirenone and ethinylestradiol under fasted conditions, it can be concluded that Bellverene 28 0.02 mg/3 mg and Jasminelle, 3.0 mg/0.02 mg, film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A significant treatment effect was observed for the $AUC_{(0-\infty)}$ of ethinylestradiol and a significant period effect for the $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of drospirenone. The observed treatment effect is considered due to the high power of the study and therefore clinically not relevant since bioequivalence has been shown. The period effect for drospirenone is neither judged to influence the conclusion of the study since only 1 case of a pre-dose level was detected and therefore no carry-over effect could be concluded.

Bioequivalence study II – 3 mg/0.03 mg strength
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 46 healthy females of childbearing potential, aged 19-44 years old. Each subject received a single dose of two tablets (2 x 3 mg/0.03 mg) of one of the 2 drospirenone/ethinylestradiol formulations under fasted conditions. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at .25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

The design is acceptable for this kind of application, the wash-out of 28 days is sufficient and the sampling period long enough. Furthermore, the sampling scheme is adequate to estimate pharmacokinetic parameters. The administration of 2 tablets was considered necessary to achieve measurable plasma ethinylestradiol levels.

Results
A total of 43 subjects finished both treatment periods of the study; a total of 3 subjects discontinued before the start of the 2nd treatment period. One of them discontinued because of fainting before dosing, another due to disallowed concomitant medication during the wash-out period and a third subject due to difficulty with blood collection during period 1.

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

Treatment N=43	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	0.9 ± 0.2	1.0 ± 0.2	65 ± 12	1.5 (0.83-4.0)	32.7
Reference	0.9 ± 0.2	0.9 ± 0.2	64 ± 13	1.25 (0.75-4.0)	31.9
***Ratio (90%**	1.05	1.06	1.01	--	--

CI)	(1.03-1.07)	(1.04-1.08)	(0.96-1.06)		
$AUC_{0-\infty}$ 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=43	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1.3 ± 0.4	1.5 ± 0.4	0.15 ± 0.04	1.5 (1.0-2.5)	32.7
Reference	1.3 ± 0.4	1.4 ± 0.4	0.14 ± 42	1.5 (1.25-2.5)	31.9
***Ratio (90% CI)**	1.05 (1.01-1.08)	1.05 (1.02-1.08)	1.01 (0.98-1.04)	--	--
$AUC_{0-\infty}$ 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 drospirenone and ethinylestradiol under fasted conditions, it can be concluded that Bellverene 28 0.03 mg/3 mg and Jasmine 3.0 mg/0.03 mg, film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

There were no pre-dose levels. A treatment effect was observed for AUC_{0-t} and $AUC_{0-\infty}$ for both ethinylestradiol and drospirenone. For drospirenone alone a significant period effect was observed for AUC_{0-t} and $AUC_{0-\infty}$. The observed treatment effect is considered due to the high power of the study and therefore clinically not relevant since bioequivalence has been shown.

Drospirenone/ethinylestradiol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of the active substances. 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 studies have 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 drospirenone/ethinylestradiol was first approved in 2000, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of drospirenone/ 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 SPCs approved during the decentralised procedure is in accordance with that accepted for the reference products Yasmin 28 and Yasminelle 28.

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 was performed on the leaflet of the 0.03 mg/3 mg strength, and 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.
The results of the first round of testing met the study objectives. Therefore, no amendments to the package leaflet were considered necessary. Also the results of the second round of testing met the study objectives. One participant commented that a line of text was missing in the flow chart. The PL mock-up was amended accordingly after the second round of testing.
In addition to the questionnaire, there were three questions at the end of the test in order to gain an opinion/feedback of the subject's interpretation of the full package leaflet. From the subject's answers to these questions and general comments, no adaptation of the package leaflet was deemed necessary.
The readability test has been sufficiently performed. For the lower strength (0.02 mg/3 mg) a justification for bridging was provided. In the bridging report differences between Daughter and Parent PL are presented along with an analysis and evidence which adequately show that these differences have little material impact on the readability. Separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Bellverene 28 0.02 mg/3 mg and 0.03 mg/3 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Yasminelle 28, film-coated tablets 0.02/3 mg and Yasmin 28, film-coated tablets 0.03/3 mg. Yasmin 28 and Yasminelle 28 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bellverene 28 0.02 mg/3 mg and 0.03 mg/3 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 April 2013. Bellverene 28 0.02 mg/3 mg and 0.03 mg/3 mg film-coated tablets were authorised in the Netherlands on 1 August 2013.

The date for the first renewal will be: 23 April 2018.

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

Quality – active substance
- The MAH committed to submit Certificates of Analysis on ethinylestradiol.

Quality - medicinal product
- The MAH committed to continue the ongoing stability studies on the production batches up to at least the proposed shelf-life.

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