Public Assessment Report

Scientific discussion

Bellvalyn 150/20 and 150/30 micrograms, film-coated tablets (desogestrel/ethinylestradiol)

NL/H/2754/001-002/DC

Date: 9 April 2014

This module reflects the scientific discussion for the approval of Bellvalyn 150/20 and 150/30 micrograms, film-coated tablets. The procedures were finalised on 15 September 2013 (higher strength) and 11 February 2014 (lower strength). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bellvalyn 150/20 and 150/30 micrograms, film-coated tablets from Egis Pharmaceuticals Plc.

The product is indicated for oral contraception.
A comprehensive description of the indication and posology is given in the SmPC.

This decentralised procedure concerns a generic application.
For the lowest strength the MAH claimed essential similarity with Mercilon 0.15/0.20 mg, tablets (NL License RVG 11508) which has been registered in the Netherlands by N.V. Organon since 19 November 1987.
For the 150/30 micrograms strength, essential similarity is claimed with the innovator product Marvelon tablets (NL License RVG 08859) which has been registered in the Netherlands by N.V. Organon since 29 May 1981. In addition, reference is made to Mercilon and Marvelon authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Czech Republic, Hunfary, Poland and Slovakia.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Bellvalyn 150/20 contains 150 micrograms of desogestrel and 20 micrograms of ethinylestradiol and is a white, round film-coated tablet of 5 mm diameter. The tablets are coded on one side “C” and on the reverse side “5”.

Bellvalyn 150/30 micrograms contains 150 micrograms of desogestrel and 30 micrograms of ethinylestradiol and is a white, round film-coated tablet of 5 mm diameter. The tablets are coded on one side “C” and on the reverse side “7”.

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

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

The placebo tablets consist of:
Tablet core - lactose monohydrate, maize starch, povidone K-30 (E1201), silica colloidal anhydrous (E551), magnesium stearate (E572)
Film-coating: hypomellose 2910 (E464), triacetin (E1518), polysorbate 80, titanium dioxide (E171), FD & C Blue 2 Aluminium lake (E132), yellow iron oxide (E172)

II.2 Drug Substances

Desogestrel
The active substance desogestrel is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder, which is practically insoluble in water. Desogestrel has six chiral centers, but does not exhibit polymorphism.

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

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

Quality control of drug substance
The drug substance is tested in accordance with the Ph.Eur. monograph with additional tests on residual solvents, any other impurity and particle size distribution. Certificates of analysis of three batches have been provided, demonstrating compliance with the specification.

Stability of drug substance
The MAH submitted stability testing results in support of a retest period of 3 years when stored under the stated conditions.

Ethinylestradiol
The active substance ethinylestradiol is an established active substance described in the Ph.Eur. It is a white to practically white crystals or powder, which is practically insoluble in water, freely soluble in ethanol and dissolves in dilute alkaline solutions. Ethinylestradiol exhibits polymorphism in the form of solvates/hydrates. The consistency and control of the anhydrate/hemi-hydrate form manufactured was adequately discussed.

The CEP procedure is used for ethinylestradiol.

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

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

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

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. A direct compression process was chosen as the manufacturing process.
The necessity for inclusion of the antioxidant vitamin E and the efficacy of the proposed level have been shown.
For the 150/30 micrograms strength the reference product used in the first bioequivalence study is Microdiol®. Microdiol is the name of the reference product in Spain which corresponds to Marvelon. The composition of innovator products is the same in most of the European countries, therefore, the innovator product used in the bioequivalence study is representative for the innovator products from all member states involved in this procedure. Although the inclusion of placebo tablets is not in line with the reference products, there is no objection from a quality point of view.
Initially the MAH applied for a biowaiver for the 150/20 micrograms strength, which could however not be granted as the reference products are based on different dossiers and because the similarity of the *in vitro* dissolution profiles of the 150/20 micrograms strength with the 150/30 micrograms strength biobatch has not satisfactorily been demonstrated. Moreover, based on the comparative *in vitro* dissolution data, equivalence between the 150/20 micrograms test and reference product cannot be concluded.
Therefore, the MAH decided to carry out a second study comparing the 150/20 microgram strength of the test product with the reference product Suavuret, which is the Spanish trademark for the reference product Mercilon. The use of the Spanish product has been sufficiently justified.

Although equivalence between the test and reference products of both strengths could be concluded based on the comparative *in vitro* dissolution data, bioequivalence was shown *in vivo,* which prevails over the *in vitro* data.
The pharmaceutical development of the product was adequately performed.

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

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

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

Stability of drug product
Bellvalyn 150/20 micrograms:
Stability data on the active drug product has been provided on three pilot-scale and three full-scale batches, stored at 25°C/60% RH (pilot-scale batches for 24 and 36 months, full-scale batches for three months),30°C/65% RH (pilot-scale batches for 12 months, full-scale batches for three months) and 40°C/75%RH (pilot-scale batches for six months, full-scale batches for three 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. The accelerated conditions demonstrate that the drug product is sensitive to elevated temperatures. Out of specification values are observed for desogestrel assay after 6 months at accelerated conditions.
A photostability study has been performed in conformity with ICH topic Q1B, demonstrating that the product is sensitive to light and the blister packaging suffices to protect the tablets from light degradation. Based on the results provided, the approved shelf life for the 150/20 micrograms strength is 24 months when stored below 30°C with the storage condition “store in the original packaging in order to protect from light”.

Bellvalyn 150/30 micrograms:
Stability data on the drug product has been provided on three full-scale batches, stored at 25°C/60% RH (up to 35 months), 30°C/65%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline.

For both strengths the accelerated conditions demonstrate that the drug product is sensitive to elevated temperatures. Out of specification values are observed for desogestrel assay after 6 months at accelerated conditions. The results under long-term and intermediate storage conditions justify the proposed shelf-life of 36 months with the storage condition “Do not store above 30°C”. A photostability study has been performed in line with ICH topic Q1B. The results demonstrate that the drug product is photostable when packed in the proposed clear transparent PVC/PVDC-Al blisters. Therefore, the storage condition “Store in the original package in order to protect from light’ is also included for both strengths.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Bellvalyn 150/20 and 150/30 micrograms, film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH committed to add at least one production batch, if manufactured, to the follow up stability program yearly.
- The MAH committed to continue the on-going stability studies with the 150/20 micrograms strength on the first three development and bioequivalence batches up to at least 36 months.
- The MAH committed to perform long-term stability studies up to at least 24 months on the first three production batches of the 150/20 micrograms strength.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Bellvalyn is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

These products are generic formulations of Mercilon and Marvelon, which are available on the European market. Reference is made tot the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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.

IV.2 Pharmacokinetics

For this generic application, the MAH initially submitted one bioequivalence study in which the pharmacokinetic profile of the test product Bellvalyn 150/30 micrograms (Egis Pharmaceuticals Plc, Hungary) is compared with the pharmacokinetic profile of the reference product Microdiol® 0.03/0.15 mg tablets (Merck Sharp & Dohme de España, S.A., Spain).

For the 150/20 micrograms product, the MAH initially applied for a biowaiver. This biowaiver could however not be granted for the lower strength, as the reference products are based on different dossiers (Mercilon and Marvelon). Moreover, the similarity of the *in vitro* dissolution profiles of the 150/20 micrograms strength with the 150/30 micrograms strength biobatch had not satisfactorily been demonstrated. Therefore, the MAH decided to conduct a second bioequivalence study with Bellvalyn

150/20 micrograms (Egis Pharmaceuticals Plc, Hungary) versus Suavuret® 0.02/0.15 mg tablets (Merck Sharp & Dohme de España, S.A., Spain).

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 analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used for the pharmacokinetic calculations and statistical evaluation are considered acceptable.
The design and results of both studies are discussed below.

Bioequivalence studies

Study I – 150/20 micrograms

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy females of child bearing potential or non-post-menopausal females with tubal ligation, aged 20-45 years. Each subject received a single dose (150/20 micrograms) of one of the 2 desogestrel/ethinylestradiol formulations. There were 2 dosing periods, separated by a washout period of 28 days.

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

Bioequivalence will be based on the active metabolite 3-keto-desogestrel. Measurement of 3-keto-desogestrel will be truncated at 72 hours as a result of its long half life.

The study design is acceptable. The sampling period and sampling scheme are adequate to properly estimate pharmacokinetic parameters. Desogestrel is rapidly absorbed and completely converted into 3-keto-desogestrel. Measurement of the metabolite 3-keto-desogestrel is justified by the achievement of non measurable plasma concentrations of the parent compound desogestrel in this study. Food does not interact with the absorption of desogestrel and ethinylestradiol. A study under fasted conditions is therefore sufficient.

Results
Fifty-six subjects were included in the statistical analyses. There was 1 subject who withdrew consent and there were 2 subjects withdrawn due to impossibility to obtain blood samples and receiving concomitant medication that could have impact on the pharmacokinetic profile of desogestrel. Another subject was excluded from the analysis due to pre-dose levels of more than 5% of the C_{max}. The reasons for drop-out are acceptable.

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

Treatment N=56	**AUC_{0-72}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	463 ± 150	503 ± 166	45 ± 13	1.5 (1.0-2.5)	--
Reference	475 ± 164	514 ± 175	48 ± 13	1.5 (1.0-3.0)	--
***Ratio (90% CI)**	0.98 (0.95-1.01)	0.98 (0.95-1.02)	0.93 (0.90-0.96)	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 3-keto-desogestrel under fasted conditions.

Treatment N=56	AUC_{0-72} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h	$t_{1/2}$ h
Test	9908 ± 3385	--	1421 ± 442	1.25 (1.0-4.0)	--
Reference	10471 ± 3499	--	1525 ± 433	1.5 (1.0-4.0)	--
***Ratio (90% CI)**	0.93 (0.91-0.97)	--	0.92 (0.87-0.97)	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Study II – 150/30 micrograms

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy females of childbearing potential or pre-menopausal females with tubal ligation between 21 and 45 years of age. Each subject received a single dose (150/30 micrograms) of one of the 2 desogestrel/ethinylestradiol formulations. There were 2 dosing periods, separated by a washout period of 28 days.

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

Bioequivalence will be based on the active metabolite 3-keto-desogestrel. Measurement of 3-keto-desogestrel is truncated at 72 hours as a result of its long half life.

The study design is acceptable. The sampling period and sampling scheme are adequate to properly estimate pharmacokinetic parameters. Desogestrel is rapidly absorbed and completely converted into 3-keto-desogestrel. Measurement of the metabolite 3-keto-desogestrel is justified by the achievement of non measurable plasma concentrations of the parent compound desogestrel in this study. Also the fasted conditions are acceptable, as the product can be taken without reference to food intake.

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

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

Treatment N=58	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h	$t_{1/2}$ h
Test	710 ± 249	772 ± 356	69 ± 21	1.5 (1.0-2.5)	--
Reference	711 ± 215	754 ± 220	74 ± 22	1.5 (1.0-2.25)	--
***Ratio (90% CI)**	0.99 (0.95-1.03)	1.00 (0.95-1.05)	0.93 (0.89-0.96)	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to 72 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 3-keto-desogestrel under fasted conditions.

Treatment N=58	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h	$t_{1/2}$ h
Test	9764 ± 3848	--	1340 ± 391	1.25 (0.7-3.0)	--
Reference	10229 ± 4526	--	1409 ± 490	1.5 (1.0-4.0)	--
***Ratio (90% CI)**	0.97 (0.94-0.99)	--	0.99 (0.91-1.04)	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_0 and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence studies Bellvalyn 150/20 and 150/30 micrograms are considered bioequivalent with Microdiol® and Suavuret® tablets, respectively.

There were no serious or significant adverse events reported during the studies. Both formulations were well tolerated, with no major side effects.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bellvalyn 150/20 and 150/30 micrograms tablets. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The MAH has laid down the following safety concerns:

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

Routine pharmacovigilance activities will be applied. This is considered appropriate.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Mercilon and Marvelon. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bellvalyn 150/20 and 150/30 micrograms, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Mercilon 0.02/0.15 mg and Marvelon 0.03/0.15 mg tablets. 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 for both strengths.

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 Bellvalyn 150/20 and 150/30 micrograms, film-coated tablets with the reference products, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 15 September 2013 for the higher strength and on 11 February 2014 for the 150/20 micrograms strength.

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