Public Assessment Report

Scientific discussion

Names of the Products:
Amarosa®, Federia®, Eslarila®, Inkodess®, Everissa®, Kylixa®, Tentacia®, Minkian®, Selikyne,
Amarosa Continuous®, Federia Continuous®, Eslarila Continuous®, Indokess Continuous®

Drospirenone + Ethinylestradiol 3 mg/0.02 mg film-coated tablets (21 active)
Drospirenone + Ethinylestradiol 3 mg/0.02 mg film-coated tablets (24 active + 4 placebo)
Drospirenone + Ethinylestradiol 3 mg/0.02 mg film-coated tablets (21 active + 7 placebo)

Procedure numbers:

HU/H/0273-0276/001/DC, HU/H/0283-0291/001/DC

Applicant:

Gedeon Richter Plc.

Date: 23 August 2012

This module reflects the scientific discussion for the approval of drospirenone/ethinylestradiol 3 mg/0.02 mg film-coated tablets.
The procedure was finalised at 21 March 2011.
For information on changes after this date please refer to the module 'Update'.

Content

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal products for human use and on the Amendment of other Regulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the Member State concerned.

In this Decentralised Procedure application the Reference member state, RMS was Hungary, while the concerned member states, CMS were as follows:

Procedure number	Product name	CMS
HU/H/0273/001/DC	Amarosa	UK
HU/H/0274/001/DC	Valdorin	BE, DE, FR, LU, NL, SE
HU/H/0275/001/DC	Eslarila	FR, UK, DE
HU/H/0276/001/DC	Inkodess	DE
HU/H/0283/001/DC	Everissa*	UK
HU/H/0284/001/DC	Kylixa	BE, DE, LU, NL, SE
HU/H/0285/001/DC	Tentacia**	FR. IT
HU/H/0286/001/DC	Minkian	DE
HU/H/0287/001/DC	Selikyne	DE, FR, UK
HU/H/0288/001/DC	Amarosa 28	UK
HU/H/0289/001/DC	Valdorin 28	DE, FR, SE
HU/H/0290/001/DC	Eslarila 28	DE, FR, UK
HU/H/0291/001/DC	Indokess 28	DE

Its name at the time of the application was
*Mezilor
**Doriang

The concerned the generic version of drospirenone/ethinylestradiol 3 mg/0.02 mg film-coated combination tablets. The Applicant: Gedeon Richter Plc. stated that this product has been developed to be essentially similar to the original product Yasminelle film-coated tablets of Bayer Schering Pharma.

Drospirenone/ethinylestradiol is a combined oral contraceptive indicated for prevention of pregnancy in women.

The contraceptive effect of drospirenone 3 mg + ethinylestradiol 0.02 mg 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.

Drospirenone is an analogue of the antimineralocorticoid spironolactone with antimineralocorticoid, progestogenic and antiandrogenic activity

Ethinylestradiol is a potent synthetic estrogen, closely related to the human estrogen, estradiol. It exerts its action by binding to the estrogen receptor, which is present in many different tissues.

Drospirenone/ethinylestradiol therapy consists in a single dose of 3 mg/0.02 mg once daily for 21 or 24 consecutive days per cycle followed by 7 tablet free days or placebo tablet for 7 or 4 days.

Since the application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application) it contained no new clinical or preclinical data, other than supporting literature where necessary.

II. QUALITY ASPECTS

II.1 Introduction

The application of drospirenone/ethinylestradiol 3 mg/0.02 mg film-coated tablets was based on Article 10.1 of Directive 2001/83/EC "Generic application". The Applicant stated that this product has been developed to be essentially similar to the original product Yasminelle film-coated tablets of Bayer Schering Pharma.

The drug product has been developed as low-dose, combined, monophasic oral contraceptives containing the known active substances drospirenone and ethinylestradiol.

Drospirenone/ethinylestradiol therapy consists in a single dose of 3 mg/0.02 mg once daily for 21 or 24 consecutive days per cycle followed by 7 tablet free days or placebo tablet for 7 or 4 days.

II.2 Drug Substance

The drug product has two active substances: drospirenone and ethinylestradiol (micronized).

II.2.1 Drospirenone

The active substance is described in the European Pharmacopoeia (Ph. Eur.).
The applicant indicated to follow an Active Substance Master File (ASMF) procedure for drospirenone drug substance. Letter of access for the ASMF has been submitted. However, during the authorization procedure a Ph. Eur. Certificate of Suitability (CEP) has been granted for this drug substance. The CEP indicates that the Ph. Eur. monograph is suitable to control the purity of the substance.

INN name: drospirenone
Chemical name: 3-oxo-6α,7α,15α,16α -tetrahydro-3'*H*,3"*H*-dicyclopropa[6,7:15,16]-17α-pregn-4-en-21,17-carbolactone

The active substance is a white or almost white crystalline powder practically insoluble in water, soluble in methanol, sparingly soluble in ethanol, freely soluble in acetone.

The manufacturing process has been adequately described; critical steps and corresponding in-process controls have been defined to ensure quality of the final substance. The in-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.

Evidence of the structure has been confirmed by mass spectra, NMR spectra and IR spectra. According to the scientific literature and experience there is no evidence of polymorphic modifications of drospirenone.

Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in respect of their origin and potential carry-over into the final drug substance.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has been set for residual solvents, residual metals and microbiological purity.

The Ph. Eur. specification includes the following tests: appearance, identification (IR), optical rotation, related substances and assay by HPLC and loss on drying tests. The specification is also in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated.

Reference materials used for the control of the substance are adequately characterized

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

GMP compliance of the API manufacturer has been demonstrated.

During the stability studies no significant changes in any parameters were observed. The proposed retest period of 2 years (indicated also on the CEP) is supported by the submitted stability data with the storage condition: “Store in the original packaging, in order to protect from light”.

II.2.2 Ethynilestradiol

The active substance is described in the European Pharmacopoeia.

The Applicant has submitted a CEP for the drug substance. It indicates that the Ph. Eur. monograph is suitable to control the purity of the substance, provided that it is supplemented with an additional HPLC test for any other detectable impurity and a test for residual solvents by GC.

INN name: ethinylestradiol
Chemical name: 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol.

The active substance is a white or slightly yellow-white crystalline powder insoluble in water, freely soluble in ethanol and soluble in dilute alkaline solution.

The manufacturing process of **micronized ethynilestradiol** is also adequately described and its quality suitably specified. The polymorphic feature is controlled and demonstrated to be stable during storage.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

The Ph. Eur. specification includes the following tests: appearance, optical rotation, and identification by IR and TLC method, related substances (HPLC), and loss on drying, assay (HPLC). Residual solvents (GC) and particle size distribution are also controlled. The specification is in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in detail in the Pharmacopoeia are adequately drawn up and sufficiently validated.

Reference materials used for the control of the substance are adequately characterized

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

The re-test period mentioned in the CEP is three years.

II.3 Medicinal Product

Drospirenone/ethinylestradiol 3 mg / 0.02 mg film-coated tablets together with the placebo tablets are packaged in blisters made of transparent PVC/PE/PVDC//Al blister. Each blister contains 21 white active film-coated tablets or 24 white active film-coated tablets + 4 green film-coated placebo tablets or 21 white active film-coated + 7 green film-coated placebo tablets, respectively.

II.3.1 The drospirenone/ethynilestradiol tablets

The aim of the development was to formulate a pharmaceutical product, which is robust, stable, in addition bioequivalent to Yasminelle, the original immediate release film-coated tablets containing drospirenone and ethinylestradiol.

Satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided. The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

As a result of development studies product with the above active ingredient composition, appearance and packaging was obtained. The used excipients were: lactose monohydrate, maize starch, pregelatinized maize starch, macrogol, poly(vinyl alcohol) grafted copolymer, magnesium stearate and as a coating Opadry White.

All excipients used comply with their respective European Pharmacopoeia monograph (with the exception of the coating agent, but its components also comply with the Ph. Eur.) Compliance of the product with the general monograph of the European Pharmacopoeia on the *Products with the risk of TSE* has been demonstrated by the applicant.

As regards dissolution and impurity profile the product was shown to be similar to the reference product.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as required in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study were presented. Certificates of analysis were also provided for the working standard used.

The tablets are packed in water-clear, transparent PVC/PE/PVDC // Aluminium foil blisters. The selected primary packaging materials comply with Ph. Eur. requirements and foodstuff legislation as confirmed by the suppliers of packaging materials.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the stability data available, the shelf-life of 24 months with the storage conditions: *Store in the original package in order to protect from light, below 25 °C* is acceptable.

The Summary of Product Characteristic, Patient Information Leaflet and label texts are pharmaceutically acceptable.

II.3.2 The placebo film-coated tablets

The development of the product has been described, the choice of excipients is justified and their functions explained. The manufacturing process development is acceptable.

A flow chart and a brief description of the manufacturing process are included.

In-process controls and critical steps are specified. Limits of critical process parameters are presented.
Process validation report is presented.

All excipients comply with the requirements of the Ph. Eur. monographs except the film-coating agent, Opadry II Green but its components also comply with the Ph. Eur. Functionality related characteristics of lactose anhydrous and magnesium stearate are specified.

The product specifications cover the appropriate parameters for this dosage form.

The batch analysis results show that the finished products meet the specifications proposed and confirm the consistency of the quality of the product.

Tablets are packed in water-clear, transparent PVC/PE/PVDC // Aluminium foil blisters.

The placebo tablets will be marketed along with a hormone containing tablets. The obtained results of stability for all batches meet the requirements of the specification at long term and intermediate conditions (36 months) and at accelerated conditions (6 months). The shelf life and storage condition of the combined product are based on the obtained stability results of both the hormone containing and the placebo tablet.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The following conclusion can be drawn: the product has been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of drospirenone and ethinyl estradiol as well are well known. As this fixed combination comprises widely used, well-known active substances, no further studies are required and the applicant provides none. The provided overview based on literature review is, therefore, appropriate.

III.2 Pharmacology

No new data have been submitted.

III.3 Pharmacokinetics

No new data have been submitted.

III.4 Toxicology

No new data have been submitted

III.5 Ecotoxicity/environmental risk assessment

Since the film-coated tablets are 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.6 Discussion on the non-clinical aspects

No new preclinical data have been submitted and therefore the application has not been subjected to a pre-clinical assessment. This is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of drospirenone and ethinyl estradiol as well are well known. As this fixed combination comprises widely used, well-known active substances, no further studies are required and the applicant provides none. The provided overview based on literature review is, thus, appropriate.

IV.2 Pharmacokinetics

IV.2.1 Drosperinone

Absorption of drospirenone is rapid and complete with an absolute bioavailability of approximately 76%. Drospirenone is about 97% bound to serum proteins, though it does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG). The pharmacokinetics of drospirenone are dose proportional following single doses ranging from 1-10 mg. Drospirenone peak plasma concentrations (Cmax) are attained approximately 1 to 3 hours after a single dose oral administration. Concomitant ingestion of food has no influence on the bioavailability of drospirenone. Drospirenone is extensively metabolized. The major plasma metabolites are the acid form of drospirenone and the 4,5-dihydro- drospirenone- 3-sulfate and are generated mostly independently of the cytochrome P450 enzymes (CYP) and are inactive. Drospirenone is metabolized only to a minor extent by CYP3A4. The elimination half-life of drospirenone is approximately 30 hours following single oral administration.

IV.2.2 Ethinylestradiol

Ethinylestradiol is rapidly and well absorbed through the gastrointestinal tract with an absolute bioavailability of approximately 40%. It is highly but non-specifically bound to serum albumin (approximately 98%). Ethinylestradiol does not bind to SHBG, but induces both SHBG and CBG synthesis. Peak plasma concentrations of ethinylestradiol are reached within 1 to 3 hours after oral dosing. 2-3 It undergoes pre-systemic conjugation both in the gut wall and the liver to estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogens. Metabolism occurs primarily by aromatic hydroxylation via CYP3A4 enzyme to form its major hydroxylated metabolite: 2- hydroxy-ethinyl estradiol. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.2 In previous studies where ethinylestradiol in combination with other hormonal components were administered, the elimination half-life of ethinyl-
estradiol was about 15 to 24 hours.2,4

The rate of absorption of drospirenone and ethinyl estradiol was slower following a high fat meal with the serum Cmax reduced by about 40% for both components. The extent of absorption (AUC) of drospirenone however, remained unchanged. In contrast the extent of absorption of ethinyl estradiol was reduced by about 20% under fed conditions.

IV.2.3 Assessment of the bioequivalence study

To support the application, the applicant has submitted the report of one randomised two-treatment, two-period, two-sequence, single dose bioequivalence study with Drospirenone/Ethinylestradiol 3 mg/0.02 mg film-coated tablets compared with Yasminelle by Bayer Schering Pharma A.G, performed in healthy female subjects under fasting conditions.

Biowaiver

Not applicable since the approval of only one strength is requested.

Study design

It was a single centre, randomised, single-dose, open-label, 2-way crossover bioequivalence study to compare the rate and extent of absorption of a test drospirenone-ethinyl estradiol 3 mg/0.02 versus Yasminelle under fasting condition. A total of 28 healthy female of childbearing potential were enrolled and dosed in the study; 26 completed the study. Pharmacokinetic population for ethinyl estradiol: Were only 25 because Subject No. 22 was excluded due to a pre-dose concentration higher than 5% of the Cmax. For drospirenone and ethinyl estradiol, samples were drawn prior to drug administration and 0.250, 0.500, 0.750, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 12.0, 16.0, 24.0, 36.0, 48.0, and 72.0 hours post-dose in each period. For drospirenone analysis only, additional blood samples were drawn at 96.0 and 120 hours post-dose (1 x 3 ml). A single oral dose of drospirenone-ethinyl estradiol as a 1 x 3 mg-0.02 mg film-coated tablet was administered in each study period. The treatment phases were separated by a washout period of 28 days.

Test and reference products

Treatment		
Treatment Identification:	**Test (A)**	**Reference (B)**
Product Name:	drospirenone-ethinyl estradiol	drospirenone-ethinyl estradiol (Yasminelle®)
Company Responsible for Manufacturing:	Gedeon Richter Plc, Hungary	Bayer Schering Pharma AG, Germany
Batch Number	U91010	WED1KJ
Manufacturing Date	01 2009	19 04 2008
Expiration Date	07 2009	04 2013
Strength:	3 mg-0.02 mg	3 mg-0.02 mg
Dosage Form:	film-coated tablet	film-coated tablet
Dose Administered:	1 x 3 mg-0.02 mg	1 x 3 mg-0.02 mg
Route of Administration:	oral	oral

Batch size of batch U91010: 330 000 pcs

Actual contents	Test tablet	Reference tablet
Drospirenone	101.1 %	106.6 %
Ethinyl estradiole	101.7 %	100.5 %

Analytical methods

Both compounds were measured by high performance liquid chromatograph coupled to tandem mass spectrometry. Full analytical validation reports are provided.

Main performance parameters

Ethinyl estradiol:

Calibration Curve Range:	1.00 to 200.00 pg/ml
Between-Run Accuracy:	QC % nominal concentrations: 101.68 to 103.07%
Between-Run Precision:	QC coefficients of variation: 3.84 to 4.26%
Within-Run Accuracy:	QC % nominal concentrations: 96.29 and 102.98%
Within-Run Precision:	QC coefficients of variation: 0.44 and 2.76%

Drospirenone

Calibration Curve Range:	250.00 to 100000.00 pg/mL
Between-Run Accuracy:	QC % nominal concentrations: 99.94 to 100.93%
Between-Run Precision:	QC coefficients of variation: 2.39 to 5.33%
Within-Run Accuracy:	QC % nominal concentrations: 97.49 to 108.82%
Within-Run Precision:	QC coefficients of variation: 0.51 to 4.62%

Pharmacokinetic Variables

The following pharmacokinetic parameters for this study were:
Primary variables: AUC0-t, Cmax
Secondary variables: AUC0-inf, Residual area, Tmax, Kel and T1/2 el.

Statistical methods

Pharmacokinetic parameters were summarized by treatment. Plasma concentrations were summarized by treatment and time point. Individual and mean plasma concentrations, as well as the plots of the plasma levels for all subjects versus time were graphically displayed for the two treatments.

ANOVA was performed on ln-transformed AUC0-t, AUC0-inf and Cmax and untransformed Kel and T1/2 el. A non-parametric test (Wilcoxon's Signed-Rank test) was carried out to compare the Tmax between treatments. Ratios of least-squares means and 90% geometric confidence intervals were calculated for ln-transformed AUC0-t, AUC0-inf and Cmax.

Inter-and intra-subject CVs were also calculated. Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (A/B) of least-squares means for ln-transformed AUC0-t and Cmax were within the acceptable range of 80% to 125% drospirenone and ethinylestradiol.

Results are shown on the next page.

Pharmacokinetic conclusion: based on these results, it can be concluded that the test drospirenone-ethinylestradiol 3 mg/0.02 mg tablet is bioequivalent to the reference Yasminelle film-coated tablet under fasting conditions.

SUMMARY OF RESULTS
DROSPIRENONE
N = 26

Pharmacokinetic Parameters

Parameters		Test (Drospirenone-Ethinyl Estradiol (A)) Mean	SD	CV (%)	Reference (Yasminelle Film-Coated Tablet (B)) Mean	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	525.41	215.19	40.96	509.62	196.50	38.56
AUC_{0-inf}	(ng·h/mL)	566.53	259.35	45.78	546.55	243.53	44.56
C_{max}	(ng/mL)	38.76	10.24	26.41	40.06	10.20	25.46
Residual area	(%)	5.99	4.47	74.59	5.32	4.21	79.15
T_{max}	(h)	1.57	0.71	44.95	1.42	0.51	35.90
T_{max}*	(h)	1.25	0.44	-	1.25	0.63	-
K_{el}	(h^{-1})	0.0264	0.0086	32.71	0.0274	0.0084	30.68
$T_{½el}$	(h)	28.94	9.33	32.24	27.66	8.77	31.71

* Medians and interquartile ranges are presented.

Drospirenone-Ethinyl Estradiol (A) vs Yasminelle Film-Coated Tablet (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	102.82%	103.55%	96.60%
90 % Geometric CI.[2]	100.25 % to 105.45 %	100.73 % to 106.45 %	92.52 % to 100.86 %
Intra-Subject CV	5.31 %	5.81 %	9.08 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Drospirenone-Ethinyl Estradiol (A)} - \text{Yasminelle Film-Coated Tablet (B)})} \times 100$

IV.1 Pharmacodynamics

Drospirenone + Ethinylestradiol 3 mg/0.02 mg 21+7 film-coated tablets are low-dose, combined, monophasic oral contraceptives. One of its active ingredients is the well-known ethinylestradiol (0.02 mg), the other active ingredient is drospirenone (3 mg), which is a progestogen. Combined oral contraceptives (COCs) act by preventing ovulation. Other effects to contribute their ovulation inhibitor action are alteration of tubal motility, endometrium morphology, and the viscosity of the cervical mucus.

In a therapeutic dosage, drospirenone also possesses antiandrogenic and mild antimineralocorticoid properties. It has no estrogenic, glucocorticoid and antiglucocorticoid activity. This gives drospirenone a pharmacological profile closely resembling the natural hormone progesterone.

IV.2 Clinical efficacy

No new efficacy data have been submitted and none are required for this type of application.

IV.3 Clinical safety

No new safety data have been submitted and none are required for this type of application.

IV.4 Discussion on the clinical aspects

Abridged, such as generic applications avoid the need for repetitive tests on and humans. For these applications the bioequivalence studies are pivotal. The study carried out concluded that the drospirenone-ethinylestradiol 3 mg/0.02 mg tablets of the present application are bioequivalent to the reference Yasminelle film-coated tablets under fasting conditions.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application contains an adequate review of published clinical data and the bioequivalence with reference product has been shown. Safety profile of drospirenone + ethinylestradiol tablets is well known and an appropriate system is available at the MAH to monitor and report clinical safety of the product. Quality of the products is adequately drawn up to support the consistent safety and efficacy of the tablets. Approval was recommended by the RMS and agreed by the CMSs.

Drospirenone 3 mg + ethinylestradiol 0.02 mg film-coated tablet has a proven chemical-pharmaceutical quality and is generic of Yasminelle tablet. Yasminelle is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Drospirenone 3 mg + ethinylestradiol 0.02 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation.

V.1 Conditions for the marketing authorisation

V.1.1 Requirements for specific post-marketing obligations

Not needed.

V.1.2 Pharmacovigilance system

The Reference Member State considers that the holder of the marketing authorisation has provided adequate written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

V.1.3 Risk Management Plan

No Risk Management Plan, as per the provisions of Volume 9A of The Rules Governing Medicinal Products in the European Union (September 2008) needs not to be submitted, given that the application has concerned a generic product with no safety concerns identified for the reference product.

V.1.5 Legal status

Prescription-only medicine

V.2 Summary of Product Characteristics (SmPC)

The holder of the marketing authorisation commits to harmonise with the SmPC of the reference one when the renewal process of the latter is finalised.

V.3. Package Leaflet and user consultation

The package leaflet and labelling are in the agreed templates and are in agreement with those of the reference product.

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 language used for the purpose of user testing was Hungarian. 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. Update: Steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Everissa tablets IB product batch size increase plus IA change of tabletting conditions	HU/H/0283/001/DC	No	28. 07. 2011	27. 08.- 2011	Approval	N
Kylixa tablets IB product batch size increase plus IA change of tabletting conditions	HU/H0284/001/DC	No	03. 08. 2011	02. 09. 2011	Approved	N
Tentacia tablets IB product batch size increase plus IA change of tabletting conditions	HU/H/0285/001/DC	No	04. 08. 2011	03. 09. 2011	Approved	N
Minkian tablets IB product batch size increase plus IA change of tabletting conditions	HU/H/0286/001/DC	No	04. 08. 2011	03. 09. 2011	Approved	N
Selikyne tablets IB product batch size increase plus IA change of tabletting conditions	HU/H/0287/001/DC	No	04. 08. 2011	03. 09. 2011	Approved	N