CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ethinylestradiol/levonorgestrel Teva 0.10 mg/0.02 mg, film-coated tablets Teva Nederland B.V., the Netherlands

levonorgestrel / 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/1380/001/DC
Registration number in the Netherlands: RVG 102388

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Pharmacotherapeutic group:	hormonal contraceptives for systemic use; progestogens and estrogens, fixed combinations
ATC code:	G03AA07
Route of administration:	oral
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of authorisation in NL:	16 December 2009
Concerned Member States:	Decentralised procedure with DE and IT
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/levonorgestrel Teva 0.10 mg/0.02 mg, film-coated tablets, from Teva Nederland B.V. The date of authorisation was on 16 December 2009 in the Netherlands. The product is indicated for oral contraception.

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

The active ingredients, levonorgestrel (LNG) and ethinylestradiol (EE) are well-known. LNG is a so-called second generation progestogen, which belongs to the gonane group derived from the C-19 nortestosterone. LNG possesses progestogenic activity. EE is a synthetic steroid with high oral estrogenic potency known since more than 60 years and is used as the estrogen component in most combined oral contraceptives (COCs). The present preparation is a monophasic COC. Due to the low estrogen content, the preparation belongs to the so-called low-dose COCs (i.e., with an EE content of no more than 35 µg per tablet).

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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Microgynon 20, coated tablets (NL License RVG 30863) which has been registered by Bayer B.V. since 11 February 2005 through MRP FI/H/334/001. In addition, reference is made to Microgynon 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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Leios Uberzogene Tabletten, registered in Germany by Wyeth Pharma. 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

Levonorgestel
The active substanblice levonorgestrel is an estashed active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to almost white crystalline powder. Levonorgestrel is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in ethanol.

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 suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification is fully in line with the currently valid Ph.Eur. monograph for levonorgestrel and the additional tests laid down in the CEP. The analytical methods used are in accordance with the CEP (and therefore with the current Ph. Eur.). Batch analytical data demonstrating compliance with the drug substance specification have been provided for one full-scale batch.

Stability of drug substance
The stability of the drug substance is not covered by the CEP. The MAH therefore performed his own stability studies. Stability data on the active substance have been provided for 3 pilot-scale batches stored at 25°C/60% RH (5 years) and 40°C/75% RH (6 months). In addition, stability data have been provided for 3 full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were stored in the packaging material used for commercial supply.
The results demonstrate that the drug substance remains stable at accelerated and long term storage conditions for all tested parameters. No specific trends were observed. The proposed re-test period of 4 years is considered acceptable when stored in the proposed packaging material. No specific storage conditions are necessary.

** 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 active substance ethinylestradiol is an established active substance described in the European Pharmacopoeia. The active substance is a white or slightly yellowish-white, crystalline powder. Ethinylestradiol is practically insoluble in water and freely soluble in alcohol. It dissolves in dilute alkaline solutions.
The CEP procedure is used for the active substance.

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 currently valid Ph.Eur. monograph for levonorgestrel and the additional tests laid down in the CEP. The analytical methods used are in accordance with the CEP (and therefore with the current Ph. Eur.). Batch analytical data demonstrating compliance with the drug substance specification have been provided.

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

Medicinal Product

Composition
Ethinylestradiol/levonorgestrel Teva 0.10 mg/0.02 mg contains as active substance 0.10 mg of levonorgestrel and 0.02 mg of ethinylestradiol. The tablets are pink and rounded.

The film-coated tablets are packed in blisters of aluminium push-thru foil and PVC/PVDC film.

The excipients are: lactose anhydrous, povidone K-30 (E1201), magnesium stearate (E572), Opadry II Pink - polyvinyl alcohol, talc (E553b), titanium dioxide (E171), polyethylene glycol 3350, red aluminium lake (E129), lecithin (E322), iron oxide red (E172), blue aluminium lake (E1329).

Pharmaceutical development
The pharmaceutical development of the product has been adequately described. The choice of excipients is justified and their functions explained. Similarity of in-vitro dissolution of the generic test product and the German reference product used in the bioequivalence studies has been demonstrated. The test and reference products used in the bioequivalence study are acceptable.

Manufacturing process
The manufacturing process is considered to be a non-standard process due to the low content of active substances. The process consists of several mixing steps, followed by compression and coating. Adequate process validation data on the product has been presented for three full-scale batches.

Excipients
The excipients comply with the Ph.Eur. These specifications are acceptable. Sufficient information on the coating mixture Opadry has been provided.

Quality control of drug product
The product specification includes tests for appearance, average weight, identification of levonorgestrel, identification of ethinylestradiol, levonorgestrel assay, ethinylestradiol assay, levonorgestrel dissolution, ethinylestradiol dissolution, levonorgestrel content uniformity, ethinylestradiol uniformity, levonorgestrel related substances, ethinylestradiol related substances, and microbial control. The release and end of shelf-life specifications are not identical. The lower levels of the assay limits are widened for the end of shelf-life specifications for both drug substances, and the limits for related substances are widened for ethinylestradiol.
The specification for dissolution is acceptable, yet should be re-evaluated when additional results are available. The MAH committed to test dissolution at both time points 45 minutes and 60 minutes. When sufficient release and stability data are available, the dissolution specification will be re-evaluated and the requirement of the Ph.Eur. will be adopted if applicable.
The in-house methods have been adequately described and validated. Batch analysis results for three full-scale batches have been provided, demonstrating compliance with the proposed release specifications.

Stability of drug product
Stability data on the product has been provided on three full-scale batches stored at 25°C/60%RH (18 months), 30°C/70%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the dosage form proposed for marketing. Minor trends are observed. However, all results comply with the approved specifications. In view of the stability results and the storage condition of the reference product, a shelf life of 2 years was granted, with an applicable storage condition of '*Do not store above 30°C*'. Photostability studies have demonstrated that the tablets are photostable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE certificates have been provided for the drug substances and for all excipients used. It is stated that the lactose anhydrous used for the tablets comes from milk of healthy animals collected under same conditions as milk suitable for human consumption. Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Microgynon coated tablets, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of levonorgestrel 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ethinylestradiol/levonorgestrel Teva 0.10 mg/0.02 mg (Teva Nederland B.V.) is compared with the pharmacokinetic profile of the reference product Leios Uberzogene Tabletten (Wyeth Pharma, Germany).

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.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-centre, open-label, randomised, two-period, two-sequence crossover bioequivalence study was carried out under fasted conditions in 34 healthy female subjects of child bearing potential, aged 18-44 years. All volunteers were Caucasian.
Each subject received a single dose of 2 tablets (0.20 mg/0.04 mg) of one of the 2 levonorgestrel/ethinylestradiol formulations. The tablet was orally administered with 240 ml water. No food was permitted from at least 10 hours before dosing until at least 6 hours after dosing. Meals were identical for both periods and standardised at 6 (lunch), 10 (light snack) and 14 (dinner) hours after the morning dose. Fluids were not allowed from 2 hours prior to dosing to 2 hours after dosing, except for the 240 ml.

taken with the medication. A total of 200 ml of low carbonated water was administered every 2 hours starting 2 hours post-dosing.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

Analytical/statistical methods
The products were administered as a single oral dose of 2 tablets to achieve sufficient measurable plasma EE concentrations to quantify at least 80% of the AUC extrapolated to infinity. The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Thirty-two subjects completed both treatment periods. Two subjects discontinued during the washout period due to personal reasons. The data set for statistical pharmacokinetic analysis of both analytes included all 32 subjects completing the study.

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

Treatment N=32	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	69335 +/- 35339	74484 +/- 38080	4941 +/- 1893	**	30.8 +/- 8.0
Reference	70521 +/- 36310	76331 +/- 39880	5707 +/- 2090	1.13 (0.50-3.03)	31.3 +/- 9.3
***Ratio (90% CI)**	0.99 (0.94-1.04)	0.98 (0.93-1.03)	0.86 (0.81-0.91)	-	-
CV (%)	12.1	12.7	13.7	-	-

$AUC_{0-\infty}$ 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*
***Data not available*

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

Treatment N=32	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1100 +/- 330	1240 +/- 356	115 +/- 50	1.00 (0.75-2.00)	20.9 +/- 11.3
Reference	1094 +/- 386	1223 +/- 396	114 +/- 48	1.25 (0.75-3.03)	18.5 +/- 5.8
***Ratio (90% CI)**	1.03 (0.96-1.10)	1.03 (0.96-1.10)	1.01 (0.94-1.09)	-	-
CV (%)	16.3	16.1	17.0	-	-

$AUC_{0-\infty}$	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 LNG and EE under fasted conditions, it can be concluded that Ethinylestradiol/levonorgestrel Teva 0.10 mg/0.02 mg and Leios Uberzogene Tabletten are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

LNG and EE may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of LNG and EE. 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.

Extrapolation of results
The bioequivalence study has been performed with two tablets instead of one. The results of the bioequivalence study with administration of a single dose with two tablets can be extrapolated to the single dose situation with one tablet. The submitted statistical analysis on linearity of C_{max} of both levonorgestrel and ethinylestradiol together with the provided data demonstrated a linear relationship between dose and C_{max} for both compounds in the applicable dose range. The proof that the pharmacokinetics of EE and LNG are linear in the applicable dose range was established with respect to C_{max} but not for AUC. However, as no problems were encountered with respect to bioavailability in the use of two tablets instead of one, a small deviation from linearity of AUC will not influence bioequivalence.
In addition, the choice of using two tablets instead of one tablet in the bioequivalence study with regard to the used analytical method has sufficiently justified. Therefore, bioequivalence of test and reference product regarding the rate and extent of absorption of both levonorgestrel and ethinylestradiol has been shown using the 0.80-1.25 acceptance range.

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 levonorgestrel and ethinylestradiol was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of LNG+EE can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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

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 consisted of two rounds with 10 participants each. After the first round of testing 80% of the participants was able to locate and understand the information in the package leaflet. Some modifications were made to the leaflet and in the second round each question has been answered correctly by at least 81% of the participants.

The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The test results were satisfactory. The conclusions are clear and concise.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ethinylestradiol/levonorgestrel Teva 0.10 mg/0.02 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Microgynon coated tablets. Microgynon 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.

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 LNG and EE containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ethinylestradiol/levonorgestrel Teva 0.10 mg/0.02 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 9 June 2009. Ethinylestradiol/levonorgestrel Teva 0.10 mg/0.02 mg was authorised in the Netherlands on 16 December 2009.

A European harmonised birth date has been allocated (27 March 1997) and subsequently the first data lock point for LNG+EE is March 2012. The first PSUR will cover the period from June 2009 to March 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 26 November 2012.

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

Quality - medicinal product

- The MAH committed to test dissolution at both time points 45 minutes and 60 minutes. When sufficient release and stability data are available, the dissolution specification will be re-evaluated and the requirement of the Ph.Eur. will be adopted if applicable.

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
COC	Combined Oral Contraceptive
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EE	Ethinylestradiol
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
LNG	Levonorgestrel
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
Withdrawal of marketing authorisation in AT, ES and IE	--	Withdrawal	--	1-7-2009	Approval	N
Change to batch release arrangements and quality control of the finished product; addition of a manufacturer responsible for batch release; not including batch control/testing.	NL/H/1380/ 001/IA/001	IA	19-8-2009	2-9-2009	Approval	N
Change to batch release arrangements and quality control of the finished product; addition of a site where batch control/testing takes place.	NL/H/1380/ 001/IA/002	IA	19-8-2009	2-9-2009	Approval	N
Addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms.	NL/H/1380/ 001/IA/003	IA	19-8-2009	2-9-2009	Approval	N
Addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms.	NL/H/1380/ 001/IA/004	IA	19-8-2009	2-9-2009	Approval	N
Addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms.	NL/H/1380/ 001/IA/005	IA	19-8-2009	2-9-2009	Approval	N
Deletion of a manufacturing site responsible for batch release.	NL/H/1380/ 001/IA/006	IA	19-8-2009	2-9-2009	Approval	N
Change in batch size of the finished product; up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation.	NL/H/1380/ 001/IA/007	IA	22-1-2010	5-2-2010	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms.	NL/H/1380/ 001/IA/008	IA	22-1-2010	5-2-2010	Approval	N
Change in the (invented) name of the medicinal product.	NL/H/1380/ 001/IB/009	IB	30-6-2010	30-7-2010	Approval	N
Change in the name and/or address of the marketing authorisation holder (address MAH in the Netherlands).	NL/H/1380/ 001/IA/010	IB	16-11-2010	16-12-2010	Approval	N
Extension of the shelf life of the finished product.	NL/H/1380/ 001/IB/011	IB	18-2-2011	20-3-2011	Approval	N
Introduction of DDPS.	NL/H/1380/ 001/WS/ 012	WS	28-10-2011	28-11-2011	Approval	N
Fulfilment of the commitment to test dissolution at both time points 45 minutes and 60 minutes.	NL/H/1380/ 001/IB/013	IB	10-4-2012	10-5-2012	Approval	N
List of changes: • SPC: new QRD-template • PL: new QRD-template • warning included for Red aluminium lake (E 129) according to Excipients Guideline (SPC, PIL, Outer Packaging) • warning included for Lecithin (from soya) according to Excipients	NL/H/1380/ 001/IB/014	IB	9-5-2012	8-8-2012	Approval	N

Guideline (PIL, Outer Packaging) • SPC: amended according to PIL (4.4 Warnings, Vascular Disorders) • PIL: amended according to SPC (Warnings and precautions)						
Change in the name of the medicinal product in the Netherlands.	NL/H/1380/ 001/IB/015	IB	8-5-2012	7-6-2012	Approval	N
Deletion of a manufacturing site of a secondary packager, update in the Ph. Eur. Certificate of Suitability of the active substance ethinyl-estradiol granted by the EDQM for an already approved active substance manufacturer. Change in the active substance specification of ethinylestradiol presented by the dossier developer Chemo in order to comply with the current relevant monograph of the Ph. Eur. tightening of the approved limits for the residual solvents in the finished product manufacturer`s active substance specification for ethinylestradiol. Addition of the test parameter “melting range” to the common active substance specification for ethinylestradiol.	NL/H/1380/ 001/IA/016/ G	IA/G	5-6-2013	5-7-2013	Approval	N
The inclusion of the statements of ADR reporting to the product information.	NL/H/1380/ 001/IA/017	IA	10-10-2014	9-11-2014	Approval	N
Introduction of the Pharmaco-vigilance System Master File (PSMF).	NL/H/1380/ 001/IA/018/ G	IA/G	8-6-2015	8-7-2015	Approval	N