CBG MEB

Public Assessment Report

Scientific discussion

Nhytideta 0.075 mg/0.020 mg and Nhytida 0.075 mg/0.030 mg tablets

(gestodene/ethinylestradiol)

NL/H/2961/001-002/DC

Date: 21 October 2015

This module reflects the scientific discussion for the approval of Nhytideta 0.075 mg/0.020 mg and Nhytida 0.075 mg/0.030 mg tablets. The procedure was finalised on 11 December 2014. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Nhytideta 0.075 mg/0.020 mg and Nhytida 0.075 mg/0.030 mg tablets from Laboratorios León Farma, S.A.

The product is indicated for oral contraception.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Meliane 0.075 mg/0.020 mg tablets and Gynovin 0.075 mg/0.030 mg tablets, which have been registered in Spain by Bayer Hispania, S.L. since 11 April 1998 and 1 February 1992, respectively.
The Dutch reference product for the 0.075 mg/0.020 mg strength, Meliane® from Bayer (NL License RVG 18242) has been withdrawn from the Dutch market on 31 December 2007. The Dutch reference product for the higher strength is Femodeen® 0.075 mg/0.030 mg coated tablets from Bayer B.V. (NL License RVG 12582). This product was withdrawn on 30 June 2014.

The concerned member states (CMS) involved in this procedure were Austria, Portugal (only 0.075 mg/0.030 mg) and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Nhytideta 0.075 mg/0.020 mg is a round, white tablets, with a diameter of 5.7 mm approximately. The white tablet is debossed with a '*C'* on one side and '*34'* on the other side.
Nhytida 0.075 mg/0.030 mg is a round, white tablets, with a diameter of 5.7 mm approximately. The white tablet is debossed with a '*C*' on one side and '*33*' on the other side.

The tablets are packed in clear to slightly opaque transparent - PVC/PVdC-Al blisters. Each blister contains 21 tablets.

The excipients are: lactose monohydrate, microcrystalline cellulose, povidone K-30, magnesium stearate, polacrilin potassium.

The compositions are the same for both tablets, except for the amount of ethinylestratiol.

II.2 Drug 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 crystalline powder.

The CEP procedure is used for the active substance ethinylestradiol. 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 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 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 demonstrating compliance with the drug substance specification have been provided for three batches.

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.

Gestodene
The active substance gestodene is an established active substance described in the European Pharmacopoeia. Gestodene is a white or yellowish, crystalline powder, which is practically insoluble in water, freely soluble in methylene chloride, soluble in methanol and sparingly soluble in ethanol 96%. Gestodene exhibits isomerism and polymorphism. Polymorphic form I is used. The CEP procedure is also used for the active substance gestodene.

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 gestodene with additional tests for residual solvents and particle size. 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 batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches. The batches were stored at 25ºC/60% RH (24 months) and at 40ºC/75% RH (6 months). All stability data reported comply with the proposed specification. No trends or significant changes are observed. In view of the provided stability data, the claimed re-test period of 36 months is acceptable. No special storage conditions are required.

II.3 Medicinal Product

Pharmaceutical development
The product development objective of the active tablets was to develop a film-coated tablet that would be bioequivalent to the medicinal products Meliane® and Gynovin®. The choice of excipients is justified and their functions explained. Sufficient information on polymorphism as well as information on the particle size distributions of both substances in the biobatch has been provided.
The formulation development has been sufficiently described. The active tablets will be manufactured by wet granulation. This process was chosen on the basis of *in-vitro* performance, batch homogeneity and impurity profile on accelerated conditions.
Dissolution profiles at three different pH's (pH 6.8, pH 4.5 and pH 1.2) were determined for test and reference batches used in the bioequivalence study. More than 85% of drug was released in 15 minutes in all three dissolution media for the test products. The dissolution of the reference products is slower and dissolution profiles of test and reference products can not be compared. The reason for the difference in dissolution profiles between test and reference product, has been sufficiently addressed and justified. The container closure system (PVC-PVdC/aluminium blisters) is usual for this type of dosage form.

Manufacturing process

The tablets are manufactured by wet granulation. The active substances ethinylestradiol and gestodene (both micronized) are mixed with lactose monohydrate, polacrilin potassium and microcrystalline cellulose. Purified water and povidone K-30 are added (granulation). The wet mass is dried and granules are calibrated. Magnesium stearate is added and thereafter, the lubricated blend is compressed into tablets and packed in blister packs. The manufacturing process has been described in sufficient detail. The manufacturing process has been adequately validated according to relevant European Guidelines.

Control of excipients
All excipients are tested in accordance with their respective Ph.Eur. monograph, except for polacrilin potassium, which is only described in the USP and tested accordingly. The specifications are acceptable.

Quality control of drug product
The active drug product specification includes tests for appearance, identification, dissolution, assay, related substances, content uniformity (release only) and microbial control. For appearance, dissolution and microbial control, the shelf-life limits are the same as the release limits. For assay, the shelf-life limit is wider than the release limit, which is supported by stability data. The release limits for all known and unknown individual impurities are acceptable. The limit for the dissolution rate is in line with the dissolution rate of the biobatch.
The analytical methods have been adequately described and validated. The HPLC methods for assay and related substances are considered stability indicating.
Batch analytical data for three batches of both strengths have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data have been provided on three batches for both strengths. The batches were stored at 25°C/60% RH (18 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. The batches were stored in transparent PVC/PVdC-Al blisters.
An upward trend is seen for all impurities related to both active substances and a downward trend for the assay of both active substances is noticed. For the 0.075 mg/0.020 mg strength, under accelerated conditions after 6 months out of specifications are seen for the gestodene assay. Under long-term and intermediate conditions, this impurity remains within specification. Therefore the storage condition of the tablets of the 0.075 mg/0.020 mg strength is restricted to “Store below 30ºC”. This temperature storage restriction has been laid down for the 0.075 mg/0.030 mg strength as well.
In view of the provided stability data, the proposed shelf-life of 21 months is acceptable. In view of the photostability testing results, the following has been added to the storage claim: “Keep blister in the outer carton, in order to protect from light”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE declaration has been provided by the applicant for lactose monohydrate as it is of animal origin. 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 Nythideta and Nhytida have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Nythideta/Nhytida 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 Meliane 0.075 mg/0.020 mg tablets and Gynovin 0.075 mg/0.030 mg tablets, which are available on the European market. Reference is made to 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

Gestodene 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, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence study in which the pharmacokinetic profile of the test products Nhytideta 0.075 mg/0.020 mg and Nhytida 0.075 mg/0.030 mg (Laboratorios León Farma, S.A., Spain) is compared with the pharmacokinetic profile of the reference products Meliane 0.075 mg/0.020 mg and Gynovin 0.075 mg/0.030 mg tablets (Bayer Hispania, Spain).

The choice of the reference products in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Bioequivalence study I - 0.075 mg/0.020 mg strength

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy female subjects, aged 24-45 years. Each subject received a single dose (0.075 mg/0.020 mg) of one of the 2 gestodene/ethinylestradiol formulations. The tablet was orally administered with 240 ml water after an overnight fast 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 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 and 60 hours after administration of the products. For gestodene only, an additional blood sample was taken at 84 hours post-dose.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable. As this product can be taken regardless food intake, a study under fasting conditions is justified.

Analytical/statistical methods
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

Two subjects were withdrawn from the study due to significant adverse events (pregnancy). One subject was withdrawn due to concomitant therapy required for adverse event. In accordance with the study protocol, data from all 29 subjects who completed the study and for whom the PK profile could be adequately characterized were used for PK and statistical analyses.

Table 1: Summary of pharmacokinetic parameters for gestodene for each treatment

Gestodene

Pharmacokinetics Parameters	Arithmetic Mean (+/-SD)[1]	
	Test product	Reference product
$AUC_{(0-t)}$ (pg•hr/mL)	28492.41 (13526.33)	27964.65 (12960.46)
AUC(0-∞) (pg•hr/mL)	30764.11 (13765.46)	29904.04 (13119.13)
Cmax (pg•hr/mL)	3300.12 (983.93)	3561.77 (1070.91)
Tmax (hr)[2]	0.750 (0.500, 1.50)[2]	0.750 (0.500, 1.50)[2]

[1] Arithmetic means (+/-SD) may be substituted by Geometric Mean (+/-CV%)
[2]Median, (Min, Max)

Table 2: Summary of pharmacokinetic parameters for ethynilestradiol for each treatment

Ethinyl estradiol

Pharmacokinetics Parameters	Arithmetic Mean (+/-SD)[1]	
	Test product	Reference product
$AUC_{(0-t)}$ (pg•hr/mL)	423.35 (116.69)	416.37 (102.21)
AUC(0-∞) (pg•hr/mL)	465.19 (130.42)	452.13 (106.80)
Cmax (pg•hr/mL)	45.08 (11.85)	46.54 (11.76)
Tmax (hr)[2]	1.27 (0.750, 2.00)[2]	1.50 (0.750, 3.00)[2]

[1] Arithmetic means (+/-SD) may be substituted by Geometric Mean (+/-CV%)
[2]Median, (Min, Max)

Table 3: Comparisons of pharmacokinetic parameters (gestodene)

Gestodene

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-t)}$ (pg•hr/mL)	102.07%	94.73 % to 109.97 %	16.78 %
AUC(0-∞) (pg•hr/mL)	103.15 %	96.08 % to 110.74 %	15.96 %
Cmax (pg•hr/mL)	93.28 %	87.18 % to 99.81 %	15.20 %

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.

Table 4: Comparisons of pharmacokinetic parameters (ethinylestradiol)

Ethinyl estradiol

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-t)}$ (pg•hr/mL)	101.00%	96.99% to 105.18 %	9.07 %
AUC(0-∞) (pg•hr/mL)	102.01 %	97.59 % to 106.62 %	9.91 %
Cmax (pg•hr/mL)	96.54 %	92.93 % to 100.29 %	8.53 %

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.

Bioequivalence study II - 0.075 mg/0.030 mg strength

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy female subjects, aged 28-45 years. Each subject received a single dose (0.075 mg/0.030 mg) of one of the 2 gestodene/ethinylestradiol formulations. The tablet was orally administered with 240 ml water after an overnight fast 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 0.25, 0.50, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 16, 24, 36, 48, 60, and 84 hours post-dose, in each period. For the 36-, 48, 60- hours post-dose for determination of both gestodene and ethinylestradiol, and 84-hour post-dose time points, a window of ±30 minutes was allowed for blood collection, for gestodene analysis only.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable. As this product can be taken regardless food intake, a study under fasting conditions is justified.

Analytical/statistical methods
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
Two subjects withdrew their consent, one subject was withdrawn from the study due to significant adverse events (headache and nausea). Data from all subjects who completed the study and for whom the PK profile was adequately characterized were used for PK and statistical analyses. The data set included 29 subjects for both active substances.

Table 5: Summary of pharmacokinetic parameters for gestodene for each treatment

Plasma Gestodene						
	Gestodene-Ethinyl Estradiol			Gynovin		
N	29			29		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-t} (pg•hr/mL)	36732.26	17133.07	46.64	35993.94	14751.41	40.98
AUC_{0-inf} (pg•hr/mL)	39306.40	17637.46	44.87	38512.53	15280.91	39.68
Residual Area (%)	7.30	4.03	55.21	7.02	3.65	51.94
C_{max} (pg/mL)	3633.72	1068.72	29.41	4046.69	1168.35	28.87
T_{max} [a] (hr)	0.750		0.50 - 1.75	0.750		0.50-1.43
K_{el} (1/hr)	0.0408	0.0124	30.48	0.0410	0.0113	27.44
$T_{½ el}$ (hr)	18.36	5.12	27.90	18.08	4.61	25.50

[a] Median
(Min - Max)

Table 6: Summary of pharmacokinetic parameters for ethinylestradiol for each treatment

Plasma Ethynilestradiol						
	Gestodene-Ethinyl Estradiol			Gynovin		
N	29			29		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-t} (pg•hr/mL)	705.00	202.08	28.66	692.84	213.37	30.80
AUC_{0-inf} (pg•hr/mL)	748.29	211.80	28.30	737.47	225.88	30.63
Residual Area (%)	5.84	2.20	37.73	6.06	2.16	35.68
C_{max} (pg/mL)	71.56	22.10	30.88	73.58	24.33	33.07
T_{max} [a] (hr)	1.50		1.00 - 3.00	1.50		1.00 - 2.00
K_{el} (1/hr)	0.0474	0.0100	21.17	0.0461	0.0079	17.05
$T_{½ el}$ (hr)	15.28	3.28	21.44	15.51	2.85	18.35

[a] Median
(Min - Max)

Table 7: Comparisons of pharmacokinetic parameters (gestodene)

GESTODENE					
Parameters	Treatment comparison	Ratio[1]	90% Geometric C.I.[2]	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	A - B	99.68%	95.56 - 103.97%	9.40%	39.54%
AUC_{0-inf}	A - B	100.04%	95.95 - 104.30%	9.30%	36.97%
C_{max}	A - B	89.59%	85.33 - 94.06%	10.86%	26.07%

A-B: Test (A) – Reference (B)
[1]Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)} \times 100$.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Table 8: Comparisons of pharmacokinetic parameters (ethinylestradiol)

ETHINYLESTRADIOL					
Parameters	Treatment comparison	Ratio[1]	90% Geometric C.I.[2]	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	A - B	102.56%	98.62 - 106.65%	8.72%	26.85%
AUC_{0-inf}	A - B	102.21%	98.33 - 106.24%	8.62%	26.77%
C_{max}	A - B	98.61%	93.39 - 104.12%	12.14%	28.34%

A-B: Test (A) – Reference (B)
[1]Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)} \times 100$.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence studies Nhytideta 0.075 mg/0.020 mg and Nhytida 0.075 mg/0.030 mg tablets are considered bioequivalent with Meliane 0.075 mg/0.020 mg and Gynovin 0.075 mg/0.030 mg tablets.

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 Nhytideta/Nhytida.

Summary of 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
Missing information	None

The MAH committed to comply with any (local) risk minimisation measures (educational materials for patients and HCPs) arising from the Article 31 referral for Combined Hormonal Contraception after a European Commission decision has been issued.

IV.4 Discussion on the clinical aspects

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

V. USER CONSULTATION

The readability test was carried out in order to fulfill the legal requirements of EU legislation article 50(3) and article 63(2) of Directive 2004/27/EC and Spanish Royal Decree 1345/2007 Article 29(3) and Article 36(3) which states that consultation with target groups is necessary to ensure that the package leaflet (PL) of a medicinal product is legible, clear and easy to use.
The chosen participants for the readability test represent the normal population who would use this contraceptive, in normal conditions. The range of selected subjects were: women aged between 18 and 45 years. A population of variable education levels was selected with an emphasis on lower education.
The developed questionnaire contained 20 questions specific to the content of the PL and 3 open question regarding general comments from the participants on the leaflet. The questions were designed to cover the parts of the leaflet where a clear understanding by the patient is necessary. There were sufficient questions about the critical sections.
A satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PL, and 90% of all participants can show that they understand and can act upon it. The data showed that overall the result met the passing criteria in the first and second round. No revisions to the PL were required after the first and second round of testing. The results of the test were satisfactory. The readability test has been sufficiently performed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nhytideta 0.075 mg/0.020 mg and Nhytida 0.075 mg/0.030 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Meliane 0.075 mg/0.020 mg and Gynovin 0.075 mg/0.030 mg tablets. Meliane and Gynovin 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 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 Nhytideta 0.075 mg/0.020 mg and Nhytida 0.075 mg/0.030 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 December 2014.

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