CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Annantah 0.060 mg/0.015 mg, film-coated tablets
Laboratorios León Farma S.A., Spain

gestodene/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/1902/001/DC
Registration number in the Netherlands: RVG 109161

28 June 2012

Pharmacotherapeutic group:	progestogens and estrogens, fixed combinations
ATC code:	G03AA10
Route of administration:	oral
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of authorisation in NL:	3 May 2012
Concerned Member States:	Decentralised procedure with AT, CZ, EE, HU, LT, LV, PL, RO, SK
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 Annantah 0.060 mg/0.015 mg, film-coated tablets from Laboratorios León Farma S.A. The date of authorisation was on 3 May 2012 in the Netherlands. The product is indicated for oral contraception.

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

The combination of ethinylestradiol/gestodene is widely used in monophasic or triphasic combined oral contraceptive preparations. Both hormonal components inhibit ovulation by suppressing gonadotrophin release.
Secondary mechanisms, which may contribute to the effectiveness as a contraceptive, include changes in the cervical mucus (which increase the difficulty of sperm penetration) and changes in the endometrium (which reduce the likelihood of implantation).

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Minesse 15/60 µg, film-coated tablets which has been registered in France by Wyeth Pharmaceuticals since 1999 (original product). In addition, reference is made to Minesse authorisations in the individual member states (reference product). In the Netherlands, Minesse is not registered anymore for economical reasons (withdrawal date 31 December 2004).

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 Minesse 0.06/0.015 mg tablets registered in Ireland. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance ethinylestradiol
The active substance ethinylestradiol is an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or slightly yellowish-white 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 two 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.

** 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.*

Active substance 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 does exhibit isomerism and polymorphism. Polymorphic form I is used.

The CEP procedure is used for the active substance gestodene. 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
The manufacturing process consists of six steps. The manufacturing process is described in sufficient detail. The starting material, solvents and reagents have been specified.

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 six batches, of which three were analysed with old in-house analytical methods, in force before the Ph.Eur. monograph implementation. 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.

Medicinal Product

Composition
Annantah 0.060 mg/0.015 mg contains as active substance 60 µg gestodene and 15 µg ethinylestradiol.

The medicinal product consists of blisters filled with 24 yellow active tablets and 4 white placebo tablets. Each active pill is a round, plain, yellow and film-coated tablet of 5.5 mm diameter. Each placebo pill is a white, round and biconvex tablet of 5.5 mm diameter

The film-coated tablets are packed in clear to slightly opaque transparent PVC/PVDC-Al blisters.

The excipients are:
Active tablets - lactose monohydrate, microcrystalline cellulose (E460), polacrilin potassium, magnesium stearate (E572), polyvinyl alcohol, titanium dioxide (E-171), lecithin (soya) (E322), talc, iron oxide yellow (E-172), xanthan gum (E415).
Placebo tablets - lactose monohydrate, povidone K25(E1201), sodium starch glycolate (type A), colloidal anhydrous silica (E551), colloidal aluminium oxide, magnesium stearate (E572).

Pharmaceutical development
The development of the placebo tablets is very simple and has been described briefly. The choice of the excipients is justified and their functions explained. The product development objective of the active tablets was to develop a film-coated tablet that would be bioequivalent to the medicinal product Minesse® and feasible to be manufactured. The choice of excipients is justified and their functions explained. The container closure system (PVC-PVdC/aluminium blisters) is usual for this type of dosage form.
Sufficient information on polymorphism as well as information on the particle size distributions of both substances in the biobatch has been provided.
Both wet granulation and direct compression processes were tried during the development of the final drug product. Experimental batches were tested and dissolution profiles were compared to the dissolution profile of the reference product. Eventually, a wet granulation method was chosen on the basis of in-vitro performance, batch homogeneity and impurity profile on accelerated conditions. The formulation development has been adequately described.
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. Essential similarity is proven for the test and reference product.
Instability of the product was observed, due to a component of the coating material, which was subsequently replaced by another coating material.

Manufacturing process
The drug product is manufactured by wet granulation. The manufacturing process has been described in sufficient detail.

The manufacturing process has been adequately validated according to relevant European Guidelines for a set maximum batch size. The packaging process of the active and placebo tablets together in one blister has been sufficiently described.

Control of excipients
All excipients are tested in accordance with their respective Ph.Eur. monograph, except for Opadry AMB Yellow, which is tested according to in-house procedures and polacrilin potassium, which is only described in the USP and tested accordingly. These 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. All release and shelf-life limits are acceptable.
The placebo drug product specification includes tests for appearance, mass uniformity, disintegration and microbial control. The shelf-life limits are the same as the release limits and are acceptable.
The analytical methods have been adequately described and validated. The HPLC methods for assay and related substances are considered to be stability indicating.
Batch analytical data for five validation batches of the active tablets (three batches with the “old” coating material and two batches with the “new” coating material) and one batch of the placebo tablets have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the placebo tablets have been provided for one full-scale batch, stored at 25°C/60% (18 months), 30°C/65% RH and 40ºC/75% RH (6 months). In view of the stability data presented, a shelf-life of 2 years for the placebo tablets is acceptable.
Stability data on the active drug product have been provided on five pilot-scale batches, of which three batches of tablets were coated with the “old” coating material. The batches were stored at 25°C/60% RH (24 months for the batches with the “old” coating material and 12 months for the batches with the “new” coating material), 30°C/65% RH (12 months) and 40°C/75%RH (6 months for all 5 batches). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in transparent PVC/PVdC-Al blisters.
All results remain within specification under all conditions. In view of these data, the storage condition claim “this product does not require any special temperature storage conditions” is justified. Based on the provided data, a shelf-life of 24 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
A TSE declaration has been provided for lactose monohydrate as it is of animal origin. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Minesse 0.06/0.015 mg, 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 gestodene 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

Gestodene 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 Annantah 0.060 mg/0.015 mg (Laboratorios León Farma S.A., ES) is compared with the pharmacokinetic profile of the reference product Minesse 0.06/0.015 mg tablets (Wyeth Medical, IE).

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, except for the coating material. This is acceptable.

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 28-43 years. Each subject received a single dose (0.06/0.015 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. Subjects were served a controlled meal not less than 4 hours post-dose, and at appropriate times thereafter, in each period. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected at 0.25, 0.50, 0.75, 1.0, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post-dose in each period. For gestodene analysis only, an additional blood sample was drawn 96 hours post-dose. The overall study design is considered acceptable considering the absorption rate and half-lives of the active substances.

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 did not complete the study. One subject was tested positive on pregnancy before the second period and one was tested positive on urine drug screening.

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

Treatment N=30	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	16.7 ± 6.3	19.2 ± 6.2	2.46 ± 0.83	0.75 (0.5 – 1.67)	18.7 ± 5.7
Reference	16.2 ± 7.1	18.9 ± 6.9	2.44 ± 0.96	0.75 (0.33 – 1.36)	20.2 ± 7.7
***Ratio (90% CI)**	1.06 (1.01 – 1.11)	1.04 (1.00 – 1.08)	1.02 (0.95 – 1.09)	--	--
CV (%)	10	9.4	16.1	--	--

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

**ln-transformed values*

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

Treatment N=30	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	317 ± 132	358 ± 152	33.6 ± 10.4	1.33 (0.75 – 4.0)	17.2 ± 5.1
Reference	307 ± 133	350 ± 155	31.9 ± 12.0	1.33 (0.75 – 2.0)	17.5 ± 5.2
***Ratio (90% CI)**	1.04 (0.98 – 1.10)	1.03 (0.97 – 1.09)	1.07 (1.01 – 1.14)	--	--
CV (%)	13.6	12.7	14.1	--	--

$AUC_{0-\infty}$	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 gestodene and ethinylestradiol under fasted conditions, it can be concluded that Annantah 0.060 mg/0.015 mg and Minesse 0.06/0.015 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Gestodene and ethinylestradiol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of gestodene and ethinylestradiol. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence 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

Gestodene/ethinylestradiol was first approved in 1999, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of gestodene/ethinylestradiol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC complies with the SPCs of other combined oral contraceptives that have been approved by European procedures.

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. Twenty questions were prepared to test for findability, understandability and applicability. The test consisted of a preliminary round of testing with 4 participants, followed by two rounds of testing with 10 participants each. The results of both the first and the second round of testing met the study objectives.
In addition to the questionnaire, there were three questions at the end of the test specific to the format of the PL. Two similar negative comments were made by 3 or more participants and those are discussed below:
1. Some participants mentioned that the leaflet contains too much information and suggested shortening the leaflet. However, because the leaflet must be an accurate representation of the SPC, and properly convey all safety issues and warnings, the length of the leaflet cannot be shortened without jeopardizing its content and validity.
2. Some participants mentioned that different formatting for sub-sections would benefit leaflet navigation. However, it was felt that introducing more formatting would be counterproductive, as it would make less noticeable those pieces of information that were deemed important and were emphasized with formatting different from the rest of the text.
The member states agreed with the reasoning of the testing company of not changing the leaflet.
There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Annantah 0.060 mg/0.015 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Minesse 0.06/0.015 mg tablets. Minesse 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Annantah 0.060 mg/0.015 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 February 2012. Annantah 0.060 mg/0.015 mg, film-coated tablets was authorised in the Netherlands on 3 May 2012.

The date for the first renewal will be: 30 November 2015.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached