CBG MEB

Public Assessment Report

Scientific discussion

Ditinell 0.060 mg/0.015 mg film-coated tablets

(gestodene/ethinylestradiol)

NL/H/3009/001/DC

Date: 12 January 2015

This module reflects the scientific discussion for the approval of Ditinell 0.060 mg/0.015 mg film-coated tablets. The procedure was finalised on 16 July 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ditinell 0.060 mg/0.015 mg film-coated tablets from Egis Pharmaceuticals Plc.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Ditinell 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), anhydrous aluminium oxide, magnesium stearate (E572).

II.2 Drug Substances

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 does exhibit 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 (2 batches for 48 months and 1 batch for 60 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 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% (36 months) and 40ºC/75% RH (6 months). For another batch, 12 months data under the conditions 30°C/75% RH are available. In view of the stability data presented, a shelf-life of 3 years for the placebo tablets is acceptable.

Stability data on the active drug product have been provided on five full-scale batches, of which three batches of tablets were coated with the "old" coating material. The batches were stored at 25°C/60% RH (30 months for the batches with the "old" coating material and 36 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 of batches with the "new" coating agent 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 36 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ditinell 0.060 mg/0.015 mg has 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 this medicinal product 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

This product is a generic formulation of Minesse, which is 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ditinell 0.060 mg/0.015 mg (Egis Pharmaceuticals Plc., Hungary) is compared with the pharmacokinetic profile of the reference product Minesse 0.06/0.015 mg tablets (Wyeth Pharmaceuticals, France).

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
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.

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*

Conclusion on bioequivalence study

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 study Ditinell 0.060 mg/0.015 mg is considered bioequivalent with Minesse 0.06/0.015 mg tablets.

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).

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 Ditinell.

Summary of safety concerns	
Important identified risks	• Venous thromboembolism, • Arterial thromboembolism • Benign and malign liver tumours • Breast cancer, Cervical cancer • Effect on hereditary angioedema

Summary of safety concerns	
	• 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

Although no additional risk minimisation measures are defined for gestodene containing combined hormonal contraceptives, national authorities can decide that educational material should be provided addressing VTE risk are necessary, as is the case in the Netherlands.

IV.4 Discussion on the clinical aspects

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

V. USER CONSULTATION

For the package leaflet (PL) a bridging report and focus test have been submitted. The content of the PL has been compared with the approved parent PLs for a product containing gestodene/ ethinylestradiol 0.06 mg/0.015 mg with placebo tablets (Jamyle and Annantah 0.060 mg/0.015 mg, procedures NL/H/1901-1902/001/DC). The content of the proposed PL is nearly the same as the current content of these already approved package leaflets.

The lay out was compared to the PL for a product containing levonorgestrel/ethinylestardol 0.15 mg/0.03 mg with 7 placebo tablets (NL/H/2649-2651/001/DC). The PLs differ regarding the font size, dimension of the PL the amount of columns per page and the format.

As there is a difference in the lay out between the second parent PL and the daughter PL, the MAH performed a focus test. The test consisted of a preliminary round of testing with 4 participants, followed by two rounds of testing with 10 participants each. There were 7 questions specific about the latest updates and 3 question specific to the format.
Taking into account the results for each question more than 90% of the participants were able to find the section and answered the question correctly. There were no changes made in the PL between the preliminary round and the test round, between both test rounds and after the second test round.
As all participants were able to locate the requested information with relative ease, no amendments were made to the layout either.

Taking into account the submitted bridging report and focus test, the readability has been sufficient demonstrated.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ditinell 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 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 Ditinell 0.060 mg/0.015 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 July 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