CBG MEB

# Public Assessment Report

# Scientific discussion

# Kosidina 0.060 mg/0.015 mg, film-coated tablets

# (gestodene and ethinylestradiol)

## NL/H/3320/001/DC

## Date: 29 September 2016

**This module reflects the scientific discussion for the approval of Kosidina 0.060 mg/0.015 mg, film-coated tablets. The procedure was finalised on 11 November 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

## List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| ERA | Environmental Risk Assessment |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Kosidina 0.060 mg/0.015 mg, film-coated tablets from Sandoz B.V.

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 B.V. since 14 June 1999. In the Netherlands, Minesse 15/60 µg, film coated tablets is not authorised anymore for economical reasons (withdrawal date 31 December 2007).

The concerned member states (CMS) involved in this procedure were Austria, Czech Republic, Estonia, Hungary, Italy, Latvia, Poland, Portugal, Romania, Slovenia and Slovak Republic.

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

# II. QUALITY ASPECTS

## II.1 Introduction

The Kosidina active tablet is a yellow, round, plain film-coated tablet and contains as active substances 0.060 mg of gestodene and 0.015 mg of ethinylestradiol.
The placebo tablet is a white, round, biconvex tablet without any active substances.

The tablets are packed in clear to slightly opaque transparent PVC/PVdC-Al blisters. Each blister contains 24 active tablets and 4 placebo tablets.

The excipients are for the active film-coated tablets:
*tablet core* – lactose monohydrate, microcrystalline cellulose (E460), polacrilin potassium and magnesium stearate (E572).
*coating* – polyvinyl alcohol (E1203), titanium dioxide (E171), soya lecithin (E322), talc (E553b), yellow iron oxide (E172) and xathan gum (E415).

The excipients are for the placebo tablets: lactose monohydrate, povidone K25 (E1201), sodium starch glycolate (type A), colloidal anhydrous silica (E551), anhydrous aluminium oxide and 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 substance is practically insoluble in water and freely soluble in ethanol (96%). Ethinylestradiol has only one true polymorphic form.

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 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 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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP. An additional test for a residual solvent is included. The specification is acceptable in view of the route of synthesis and various European Guidelines. Batch analytical data demonstrating compliance with this specification have been provided for four 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 Ph.Eur. 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%. The active substance exhibits polymorphism and isomerism. For this substance, polymorphic form I is manufactured. The CEP procedure was also used for gestodene.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP. Additional tests for residual solvents and particle size are included. The specification is acceptable in view of the route of synthesis and various European Guidelines. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines. The batches were stored at 25ºC/60% RH (up to 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 5 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
The only excipient of animal origin is lactose monohydrate. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Kosidina has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made

# III. NON-CLINICAL ASPECTS

## III.1 Ecotoxicity/environmental risk assessment (ERA)

Since 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 15/60 µg, film-coated tablets, 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 one bioequivalence study, which is discussed below.

## IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Kosidina 0.06 mg/0.015 mg tablets (Sandoz, the Netherlands) is compared with the pharmacokinetic profile of the reference product Minesse 0.06/0.015 (Wyeth Pharmaceuticals, France).

Bioequivalence study
*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 28-42 years. The subjects were of childbearing potential or prior-to-menopause females. Each subject received a single dose (0.060 mg/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. The subjects were served a controlled meal not less than 4 hours post-dose is each period. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and 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 after administration of the products. 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.

The product 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.

*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. One subject was withdrawn due to an item found during baggage check (facial cleanser containing salicylic acid) and the other subject for requiring concomitant therapy for a respiratory tract infection. Therefore, a total of 30 subjects were eligible for pharmacokinetic analysis.

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 |
|---|---|---|---|---|
| **Test** | 16.7 ± 6.3 | 19.2 ± 6.2 | 2.46 ± 0.83 | 0.75 (0.5 – 1.67) |
| **Reference** | 16.2 ± 7.1 | 18.9 ± 6.9 | 2.44 ± 0.96 | 0.75 (0.33 – 1.36) |
| ***Ratio (90% CI)** | 1.06 (1.01 – 1.11) | 1.04 (1.00 – 1.08) | 1.02 (0.95 – 1.09) | -- |
| **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity<br>**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration | | | | |

**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 |
|---|---|---|---|---|
| **Test** | 317 ± 132 | 358 ± 152 | 33.6 ± 10.4 | 1.33 (0.75 – 4.0) |
| **Reference** | 307 ± 133 | 350 ± 155 | 31.9 ± 12.0 | 1.33 (0.75 – 2.0) |
| ***Ratio (90% CI)** | 1.04 (0.98 – 1.10) | 1.03 (0.97 – 1.09) | 1.07 (1.01 – 1.14) | -- |
| **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity<br>**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration | | | | |

**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 Kosidina 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 Minesse 15/60 µg, film coated tablets.

- Summary table of safety concerns as approved in RMP

| | |
|---|---|
| Important identified risks | - Venous thromboembolism (VTE)<br>- Arterial thromboembolism (ATE)<br>- Benign and malign liver tumours<br>- Breast cancer, cervical cancer<br>- Effect on hereditary angioedema<br>- Disturbance of liver function<br>- Pancreatitis<br>- Increased blood pressure |
| Important potential risks | - Worsening of endogenous depression/depressed mood<br>- Crohn's disease and ulcerative colitis |
| Missing information | none |

The additional risk minimisation measures for the identified risks VTE and ATE, to remind healthcare professionals (HCPs) of the importance of recognizing the risk of a blood clot occurrence and the need to instruct patients on correct identification of signs and symptoms they need to look out for and what actions are needed to be taken, are in line with the assessment report of the Pharmacovigilance Risk Assessment Committee (PRAC) laid down in the recent Article 31 referral EMEA/H/A-31/1356 for combined hormonal contraceptives. These additional risk minimisation measures include a Patient Information Card and a Checklist for prescribers. The actual number of documents, final format, layout, and content of the materials should be agreed with the national competent authorities during the national implementation of the educational materials.

1.The Patient Information Card is instructing the patients:
- In which situations is the risk of a blood clot highest
- When to immediately seek medical attention
- What symptoms need to be addressed towards the care giver
- When should the patient inform the doctor, nurse or surgeon that she is taking Gestodene-Ethinylestradiol.

2. The Checklist for Prescribers encourages the HCPs to use this tool in conjunction with the Summary of Product Characteristics during every combined hormonal contraceptive (CHC) consultation. The HCPs are advised for which medical conditions the CHC should not be used and the HCPs are advised to discuss the suitability of a CHC with the patient. The patients should be informed about the situations when the blood clot risk is increased.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Minesse 15/60 µg, film coated tablets. 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 evaluation of the package leaflet (PL), the MAH has submitted:
- the results of a successful user test on the package leaflet (PL) of another gestodene/ethinylestradiol 0.060 mg/0.015 mg (28 film-coated tablets) product
- a focus test on the Kosidina leaflet
- a double bridging study

The focus test consisted of a preliminary round of testing with 4 participants, followed by two rounds of testing with 10 participants each. All respondents located and understood the information in the PL.

During the double bridging study the PL was compared to two approved PLs of other oral contraceptive products. Taking into account the submitted bridging reports and focus test the readability has been sufficient demonstrated.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Kosidina 0.060 mg/0.015 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Minesse 15/60 µg, film coated 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 Kosidina 0.060 mg/0.015 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 November 2015.

## 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 |
|---|---|---|---|---|---|---|
| | | | | | | |