CBG MEB

Public Assessment Report

Scientific discussion

Kosidina 0.075 mg/0.020 mg and 0.075 mg/0.030 mg 21+7, tablets

(gestodene and ethinylestradiol)

NL/H/3352/001-002/DC

Date: 29 September 2016

This module reflects the scientific discussion for the approval of Kosidina 0.075 mg/0.020 mg and 0.075 mg/0.030 mg 21+7, tablets. The procedure was finalised on 24 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

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 0.075 mg/0.020 mg and 0.075 mg/0.030 mg 21+7, 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 an application claiming essential similarity with the innovator products Meliane 0.075 mg/0.020 mg tablets (also including 7 placebo tablets) and Gynovin 0.075 mg/0.030 mg tablets (not including 7 placebo 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The Dutch reference product for the 0.075 mg/0.020 mg strength, Meliane from Bayer (NL License RVG 18242) has been withdrawn from the Dutch market on 31 December 2007.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 This product was withdrawn on 30 June 2014.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 Czech Republic, Finland, Romania and Slovenia.

The marketing authorisation for Kosidina 0.075 mg/0.020 mg has been granted pursuant to Article 10(1) of Directive 2001/83/EC.
The marketing authorisation for Kosidina 0.075 mg/0.030 mg 21+7, tablets has been granted pursuant to Article 10(3) of Directive 2001/83/EC, an hybrid application since the reference product does not contain placebo tablets.

II. QUALITY ASPECTS

II.1 Introduction

Kosidina 0.075 mg/0.020 mg is a white, round active tablet, debossed with a ‘C’ on one side and ‘34’ on the other side. Each active tablet contains as active substances 0.075 mg of gestodene and 0.020 mg of ethinylestradiol.
Kosidina 0.075 mg/0.030 mg is a white, round tablet debossed with a ‘C’ on one side and ’33’ on the other side. Each tablet contains as active substances 0.075 mg of gestodene and 0.030 mg of ethinylestradiol.
The placebo tablets are green, round and do not contain active substances.

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

For the active tablets the excipients are: lactose monohydrate, microcrystalline cellulose (E460), povidone K 30 (E1201), magnesium stearate (E572) and polacrilin potassium.

For the placebo green tablets the excipients are: lactose monohydrate, maize starch, povidone K-30, magnesium stearate, silica colloidal anhydrous, hypromellose 2910, triacetin (E1518), polysorbate 80, titanium dioxide (E171), FD&C blue 2 aluminium lake (E132) and yellow iron oxide (E172).

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

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 Ph.Eur and the CEP. An additional test for a residual solvent was 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
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 is in line with the Ph.Eur. and the CEP with additional tests for residual solvents and particle size. 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 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 (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 Products

Pharmaceutical development
The products are an established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The tablets are manufactured by wet granulation. This process was chosen on basis of *in-vitro* performance, batch homogeneity and impurity profile on accelerated conditions.
Dissolution profiles at 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 the drug product 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.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The process consist of mixing, drying, calibration, compression and packing. Process validation data on the product have been presented for three batches for both strengths.

Control of excipients
All excipients are tested in accordance with their respective Ph.Eur. monograph, except for the coating system of the placebo tablets, which is tested according to in-house procedures, and polacrilin potassium, which is described in the United States Pharmacopeia and tested accordingly. The specifications are acceptable.

Quality control of drug products
The drug product specifications for the drug products are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, dissolution, assay, related substances, content uniformity (release only) and microbial control. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Batch analytical data from three batches of both strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug products
Stability data on the placebo tablets have been provided for 2 pilot scale batches, stored at 25°C/60% (36 months) and 40ºC/75% RH (6 months). The parameters appearance, disintegration and microbial control remained within specification. In view of the stability data presented, a shelf-life of 36 months for the placebo tablets is acceptable.
Stability data have been provided on 3 batches for both strengths of the active tablets. 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 the proposed packaging.
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 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
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 substance and finished product. No post-approval commitments were made

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Kosidina is intended for 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 and hybrid formulations of Meliane 0.075 mg/0.020 mg tablets and Gynovin 0.075 mg/0.030 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

Gestodone 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 application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profiles of the test products Kosidina 0.75 mg/0.020 mg and 0.075 mg/0.030 mg (Sandoz B.V., the Netherlands are compared with the pharmacokinetic profile of the reference products Meliane 0.075 mg/0.020 mg and Gynovin 0.075 mg/0.030 tablets (Bayer Hispania, Spain).

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

Bioequivalence studies

Bioequivalence study I: 0.075 mg/0.030 mg strength
Design
A single centre, randomised, single-dose, open-label, 2-way cross-over 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. 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, 1.25, 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 after administration of the products. For gestodene analysis only, an additional blood sample was drawn 84 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

A total of 29 subjects completed all study periods and were included in the pharmacokinetic analysis. One subject was withdrawn from the study due to significant adverse events (headache and nausea) and two subjects withdrew their consent.

Table 1. 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 2. 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 3. 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: $e^{(DIFFERENCE)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Table 4. 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: $e^{(DIFFERENCE)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Bioequivalence study II: 0.075 mg/0.020 mg strength

Design

A single centre, randomised, single-dose, open-label, 2-way cross-over 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. 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, 0.5, 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 analysis only, an additional blood sample was drawn 84 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

A total of 29 subjects completed all study periods and were eligible for pharmacokinetic analysis. Two subjects were withdrawn from the study due to significant adverse events (pregnancy) and one subject due to concomitant therapy required for an adverse event.

Table 5 Summary of pharmacokinetic parameters for ethinylestradiol 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 6 Summary of pharmacokinetic parameters for ethinyl-estradiol 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 7 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 8 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.

Justification placebo tablets

The application NL/H/3352/002/DC (0.075mg/0.030 mg tablet including 7 placebo tablets) concerns an application in accordance with article 10(3) of Directive 2001/83/EC and the MAH included a justification for the addition of the placebo-tablets in the dossier of the application.
For the addition of the 7 placebo tablets in the 10(3) application for NL/H/3352/002/DC, the MAH refers to public literature in which the reference product also has 7 placebo tablets per 28-day cycle instead of a 7-day pill free interval. The published studies referred to demonstrated that the use of placebo tablets instead of a 7-day pill free interval has similar efficacy and safety in comparison to that known for combined oral contraceptives with a pill-free interval instead of placebo tablets for 7 days. The additional 7 placebo tablets instead of a pill-free interval, which variant is available for several other registered combined oral contraceptives, was developed for improvement of compliance. In conclusion, the public literature demonstrated that efficacy and safety of this product is similar to that known for combined oral contraceptives with a pill-free interval instead of placebo tablets for 7 days.

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, Kosidina 0.075 mg/0.020 mg and 0.075/0.030 mg, tablets are considered bioequivalent with Meliane 0.075 mg/0.020 mg tablets 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 Kosidina.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Venous thromboembolism - Arterial thromboembolism - Benign and malign liver tumours - Breast cancer, cervical cancer - Effect on hereditary angioedema - Disturbance 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 additional risk minimisation measures for the identified risks VTE and ATE, to remind healthcare professionals 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 action are needed to be taken, are in line with the PRAC assessment report of 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 Meliane 0.075 mg/0.020 mg and Gynovin 0.075 mg/0.030 mg. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the products are similar to the pharmacokinetic profile of these reference products. Risk management is adequately addressed. These medicinal products can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The study consisted of a pilot with 4 subjects, followed by two round with 10 participants each. The results show that the information in the PL is understandable and that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Kosidina 0.075 mg/0.020 mg and 0.075 mg/0.030 mg tablets have a proven chemical-pharmaceutical quality and are generic and hybrid 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 Kosidina 0.075 mg/0.020 mg and 0.075 mg/0.030 mg 21+7, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 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
Change in the batch size (including batch size ranges) of the finished product	NL/H/3352/ 1/IB/001	IB	12-05-2016	11-06-2016	Approved	No