CBG MEB

Public Assessment Report

Scientific discussion

Canesten Gyno 1 soft capsule, 500 mg vaginal capsules

(clotrimazole)

NL License RVG: 114223

Date: 24 October 2016

This module reflects the scientific discussion for the approval of Canesten Gyno 1 soft capsule, 500 mg vaginal capsules. The marketing authorisation was granted on 11 February 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

AE	Adverse event
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CI	Confidence Interval
CPMP	Committee for Proprietary Medicinal Products
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
EWP	Efficacy Working Party
ICH	International Conference of Harmonisation
ITT	Intent-to-treat
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PP	Per protocol
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Canesten Gyno 1 soft capsule, 500 mg vaginal capsules from Bayer B.V.

The product is indicated for the treatment of vaginitis caused by Candida spp. Symptoms include vaginal itching and burning, redness and swelling of the vulva and a white, curd-like, odourless discharge. This medicine is indicated for adults and adolescents from the age of 16.

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

This national application concerns a line extension to Canesten gyno 1 tablet, 500 mg vaginal tablets (NL License RVG 10051), which has been registered in the Netherlands since 14 June 1983.
Canesten gyno contains clotrimazole as active substance. Clotrimazole impairs the structure and function of the cytoplasmic membrane of fungi by inhibiting the synthesis of ergosterol. It has a fungistatic effect and possesses activity against various fungi and yeasts. In the Netherlands, several clotrimazole containing products are registered in various strengths and formulations for the treatment of vaginal candidiasis (10 mg/g and 20 mg/g cream; 100 mg, 200 mg and 500 mg vaginal tablets).

The application for Canesten Gyno 1 soft capsule concerns a novel pharmaceutical form (soft capsule) of vaginal clotrimazole. The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

No new non-clinical studies were submitted with this application, which is acceptable given that the product is a line extension of an approved product license containing a well-known active substance.

To support the application, data from one new clinical study were submitted, to evaluate the therapeutic equivalence of the soft gel capsule versus the vaginal tablet. No other new clinical data were submitted, which is acceptable for this line extension.

II. QUALITY ASPECTS

II.1 Introduction

Canesten Gyno 1 soft capsule contains 500 mg of clotrimazole suspended in paraffin. It is a teardrop soft capsule with a yellow opaque gelatin shell containing a homogenous suspension.

The capsule is packed in a PVC/PVDC/PVC–Al blister. The drug product is supplied with a disposable applicator.

The excipients are white soft paraffin, liquid paraffin, gelatin, glycerol, water, titanium dioxide (E171), quinolone yellow (E104), sunset yellow (E110), soy lecithin, and medium-chain triglycerides.

II.2 Drug Substance

The active substance is clotrimazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to slightly yellowish fine crystalline powder. The active substance is practically insoluble in water, freely soluble in ethanol and chloroform, sparingly soluble in ether. Two polymorphous forms are known, which differ with respect to melting point. During manufacture of clotrimazole only one is found.

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 drug substance specification is in line with the Ph.Eur. and the CEP. The drug substance specification of the active substance manufacturer contains additional requirements for particle size distribution and microbiological contamination. The full drug substance specification is applied by the drug product manufacturer. Batch analytical data demonstrating compliance with the drug substance specification of the active substance and finished product manufacturer were provided for three commercial batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Due to the experience of the drug product manufacturer with soft gelatin capsules, development focussed on the formulation of the capsule fill. The choices of the manufacturing process and packaging are justified.
The applicator consists of a body and a pestle packed in a plastic overwrap. The applicator is made of polypropylene with white pigment. The materials used are physiologically safe. Specifications and short descriptions of analytical methods were provided as well as IR spectra of the body and pestle. The applicator is CE marked.
The development of the dissolution method and the chosen test parameters has been explained. The MAH demonstrated the discriminative ability of the dissolution method by showing dissolution results of a 7 years old batch versus dissolution results of two ‘fresh’ batches.

Manufacturing process
The manufacturing process consists of gelatin mass preparation, fill preparation, encapsulation, drying, inspection, and (bulk) packaging. The manufacturing process has been adequately validated according to relevant European guidelines.
Process validation data on the product has been presented for three commercial scale batches.

Control of excipients
Except for the colouring agents quinolone yellow and sunset yellow, the excipients comply with the Ph. Eur. Specifications were provided for these colourants. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, uniformity of fill mass, average fill mass, uniformity of dosage units, disintegration, dissolution, identification of active ingredient, identification of shell colouring agents, assay of active ingredient, degradation products and microbial quality.
The proposed release and shelf life criteria differ by the fact that uniformity of fill mass, average fill mass, and identification of colouring agents of the shell are only tested at release. The acceptance criteria for the other parameters are identical at release and shelf life. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three commercial-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on one pilot- and three commercial-scale batches stored at 25°C/60% RH (commercial-scale batches: 36 months), 30°/65% RH (pilot-scale batch: 24 months, commercial-scale batches: 36 months), 30°/65% RH (pilot-scale batch: 24 months, commercial-scale batches: 36 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 PVC/PVDC/PVC-Al blisters. No significant changes or trends were observed.
The fill formulation was exposed to white light in order to force degradation of the drug substance and generate impurities to check method specificity. No significant degradation was observed. Furthermore, clotrimazole soft gelatine capsules are opacified with titanium dioxide. The fill of the capsule is not exposed to light. Therefore the finished protect does not need protection from light.
Based on the stability results, a shelf life of 3 years has been granted, without specific storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is of bovine origin. 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 MEB considers that Canesten Gyno 1 soft capsule, 500 mg vaginal capsules 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 Pharmacology, pharmacokinetics and toxicology

The pharmacological, pharmacokinetic and toxicological properties of clotrimazole are well- known. This product is a line extension of an approved product license. 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 data. Therefore, the MEB agreed that no further non-clinical studies are required.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Canesten Gyno 1 soft capsule is a line extension which is expected to substitute an available product, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

No bioavailability data are submitted for the Canesten Gyno 500 mg capsule. Reference is made to the Canesten Gyno 500 mg tablet for which it was shown that after vaginal administration of 1 tablet, low plasma clotrimazole plasma levels were observed (<10 ng/ml). In addition, high clotrimazole levels were observed in vaginal secretions. Also after application of a cream or vaginal capsule at a 500 mg dose, plasma levels were very low (< 12 ng/ml).

The SmPCs of Canesten Gyno tablet and cream indicate a low absorption after vaginal application (3 – 10% of the dose). For the Canesten Gyno 500 mg capsule it is also expected that absorption will be low and thus also the systemic exposure. The lack of a bioavailability study is acceptable.
After oral administration, an interaction is observed between clotrimazole and tacrolimus. Considering that after oral administration, high levels in the intestinal tract and a high systemic exposure compared to vaginal application can be expected, such an interaction may be unlikely in case of vaginal

application. The same statement as for the cream and tablet formulation is included in the SmPC, indicating that interactions are unknown.

IV.2 Pharmacodynamics

No new pharmacodynamic studies were conducted. Since the mechanism of action of clotrimazole is well-known and the strength of the new formulation is similar to that of the approved reference formulation this is acceptable.

IV.3 Clinical efficacy

In support of this application, the MAH conducted a clinical trial to investigate non-inferiority of the novel pharmaceutical form (soft capsule) of vaginal clotrimazole compared to the approved vaginal tablet formulation with regard to efficacy and safety.

Phase III non-inferiority study

Methodology

Study design

This study was an investigator-blinded, 2-arm, randomized, single dose, active controlled, parallel group phase III study to prove the non-inferior efficacy of a 500 mg clotrimazole soft capsule (ovule) versus a 500 mg clotrimazole vaginal tablet in vaginal candidiasis. The study was conducted at 18 centers (Germany; 11 centers and Russia; 7 centers).

Non-pregnant females aged between 14 years (Germany) or 16 years (Russia) and 50 years with clinical signs and symptoms of vulvovaginal mycosis confirmed by microscopic investigation (wet mount preparation) and a negative saline smear for Trichomonas vaginalis. An acceptable method of contraception had to be used and no antimycotic treatment within 60 days prior to visit 1 was allowed.

At screening/baseline (visit 1) clinical symptoms (itching, burning/irritation, discharge, dysuria) and signs (vaginal edema, erythema and excoriation, and vulval edema, erythema and excoriation) of vaginitis were assessed and mycological testing was performed.

Subjects meeting all inclusion criteria were then randomly assigned to receive either a single dose of clotrimazole 500 mg vaginal capsule or a single dose of clotrimazole 500 mg vaginal tablet. Study medication had to be applied, using the applicator, prior to laying down for sleep.

At visit 2 (10 to 14 days after visit 1) and at visit 3 (6 to 8 weeks after visit 1) clinical signs and symptoms of a vaginitis and a mycological tests were performed. The study was single-blind (*i.e.* investigator-blinded).

Objectives and endpoints

Primary objective

The primary objective was to demonstrate non-inferior efficacy in terms of overall responder rate defined as clinical cure and mycological cure 10-14 days (visit 2) after treatment of a single dose of clotrimazole 500 mg (vaginal capsule compared to vaginal tablet).

Secondary objectives

To demonstrate non-inferiority of clotrimazole 500 mg vaginal capsule compared to clotrimazole 500 mg vaginal tablet with regard to:

- overall responder rate 6-8 weeks (visit 3) after treatment
- clinical cure 10-14 days (visit 2) and 6-8 weeks (visit 3) after treatment
- mycological cure 10-14 days (visit 2) and 6-8 weeks (visit 3) after treatment

The primary efficacy variable was the responder rate at visit 2, defined as the rate of subjects with mycological cure and a clinical cure.

Mycological cure:

- negative microscopy (wet mount preparation and potassium hydroxide (KOH) slides of vaginal secretion taken from the posterior fornix)
- and negative mycological culture in vaginal secretion taken from the posterior fornix.

Clinical cure:

- absence of the symptoms itching and burning/irritation
- and no more than mild expressions of other symptoms (discharge, dysuria; reported by subjects) and signs (vaginal edema, erythema and excoriation, and vulval edema, erythema and excoriation; reported by the investigator)
- and no worsening of any symptoms and signs compared to baseline visit.

Clinical symptoms and signs of vaginitis were evaluated by the investigator at visit 1 (baseline), visit 2, and visit 3 using a 4-point scale (0 = not present, 1 = mild, 2 = moderate, 3 = severe).
Symptoms of vaginitis were rated by the subject at all visits and between visit 1 and visit 2 once daily at home in the subjects' diary. The symptoms of vaginitis to be assessed were itching, burning/irritation, discharge, and dysuria, using a 4-point scale (1 = normal, 2 = mild, 3 = moderate, 4 = severe).

Sample size
Approximately 440 patients (220 for each arm) were to be randomized. This would provide 80% power to detect a 15% difference responder rates between the tablet and capsule at a 2-sided 5% significance level, assuming a 60% overall response rate and 20% drop-out.

Statistical analyses and study populations
Analysis of overall responder rate at visit 2 was performed by deriving a two-sided 95%-confidence interval (CI) of the difference of response rates of the tablet and the capsule. The applicant describes two definitions of non-inferiority:

- the lower limit of the confidence interval for the response rate of the capsule had to be larger than the observed response rate of the tablet minus 15%
- the lower end of the 95% CI of the treatment difference had to be higher than -15%

Safety population: All subjects who received a dose of the trial medication.
Intent-to-treat (ITT) population: All subjects who completed the treatment and at least visit 2 and had a positive mycological test for Candida spp. at baseline.
Per-protocol (PP) population: All subjects who completed the treatment and at least visit 2, had a positive mycological test for Candida spp. at baseline and had no major protocol violations (violation of in-/exclusion criteria, lost to follow-up after Visit 2, anti-infective treatment prior to Visit 2, Visit 2 not performed within 7 to 21 days after drug administration, administration not performed according to schedule).

Results
Participant flow and numbers analysed
Overall, 465 subjects were randomized (tablets: n=228, capsule: n=237). Overall, 348 subjects (74.8%) completed the study as planned, 117 subjects (25.2%) were withdrawn, mainly because vaginal candidiasis was not confirmed.

Overall, 463 of the 465 subjects randomized received treatment and were valid for the safety population. Due to major protocol deviations, further 86 of the safety population were excluded from the ITT population, and further 11 subjects were excluded from the PP-population.

Baseline data
Only limited differences in demographic characteristics between the treatment groups were observed. For the ITT and PP populations similar mean values were obtained. There were no relevant differences between the study centers with respect to demographic values.

The most frequently observed findings in medical history were in the category 'others', and were mainly gynecological findings like e.g. hysterectomy, myoma, ectopia coli uteri or chronic adnexitis (tablet group 18.4% and soft capsule group 19.6%). Also allergies (tablet group 6.1% and capsule

group 6.4%) and findings in the gastrointestinal system (tablet group 3.9% and capsule group 6.4%) were reported.

No subject had recurrent vulvovaginal mycosis within the last 12 months. Other relevant findings in the gynecological examination were positive Candida culture 5 days prior to screening (n=1 capsule group), antibiotic treatment due to an angina tonsillaris nearly 3 weeks prior to screening (n=1 capsule group), human papilloma virus positive (n=1 capsule group).

Analyses of efficacy

Primary endpoint

Non-inferiority with regard to overall responder rate 10-14 days after treatment of the capsule compared to the tablet formulation was demonstrated in both the PP and ITT population. The responder rate 10-14 days after treatment in the capsule group was larger than the observed responder rate in the tablet group (table 1). The results were similar for the ITT population: 126/192 subjects (65.6%) in the tablet group and 134/185 subjects (72.4%) in the capsule (ovule) group were responders (treatment difference 6.8% (-7.5%, 21.2%)).

Table 1: Overall response at visit 2 (PP population)

	- Tablets - N=186 n (%)	- Ovules - N=180 n (%)
Number of responders (n (%))	123 (66.1%)	132 (73.3%)
95% CI	(59.2%, 73.2%)	(66.6%, 80.1%)
Difference ovules-tablets (95% CI)	7.2% (-7.3%, 21.7%)	

CI = confidence interval

Secondary endpoint

- Overall responder rate at visit 3

At visit 3 the overall response rate was similar to visit 2 in the capsule group and slightly higher than at visit 2 in the tablet group. The response rate was higher in the tablet group (table 2). The results were similar for the PP population: 128/169 subjects (75.7%) in the tablet group and 124/169 subjects (73.4%) in the capsule (ovule) group were responders (treatment difference -2.4% (-17.0%, 12.2%).

Table 2: Overall response at visit 3 (ITT population)

	- Tablets - N=192 n (%)	- Ovules - N=185 n (%)
Number of subjects with available data	184	178
Number of responders (n (%))	138 (75.0%)	129 (72.5%)
95% CI	(68.5%, 81.5%)	(65.6%, 79.3%)
Ovules-tablets (95% CI)	-2.5% (-16.7%, 11.7%)	

CI = confidence interval

- Clinical signs and symptoms of vaginitis at visit 2 and 3

Most subjects in both treatment groups were free of signs or symptoms of vaginitis at 2 weeks after treatment. The responder rates were similar for both treatment groups (84.4% and 88.1% for clinical symptoms and 96.9% and 98.4% for signs of vaginitis for the tablet and capsule group, respectively). At 6 to 8 weeks after drug administration the cure rates for clinical symptoms further increased in both treatment groups and remained similar for the signs of vaginitis.

Table 3: Response rates for clinical symptoms and signs of vaginitis (ITT population)

	- Tablets - N=192 n (%)	- Ovules - N=185 n (%)	- Tablets - N=192 n (%)	- Ovules - N=185 n (%)
Clinical symptoms	Visit 2		Visit 3	
No. of subjects with available data	192	185	185	180
Number of responders (n (%))	162 (84.4%)	163 (88.1%)	172 (93.0%)	167 (92.8%)
95% CI	(79.0%, 89.8%)	(83.2%, 93.0%)	(89.0%, 96.9%)	(88.7%, 96.8%)
Ovules-tablets (95% CI)	3.7% (-8.2%, 15.7%)		-0.2% (-10.6%, 10.2%)	
Clinical signs	Visit 2		Visit 3	
Number of subjects with available data	192	185	185	180
Number of responders (n (%))	186 (96.9%)	182 (98.4%)	183 (98.9%)	171 (95.0%)
95% CI	(94.2%, 99.6%)	(96.3%, 100.5%)	(97.2%, 100.7%)	(91.5%, 98.5%)
Ovules-tablets (95% CI)	1.5% (-6.6%, 9.6%)		-3.9% (-12.3%, 4.5%)	

CI = confidence interval

- Mycological cure at visit 2 and 3

At 10-14 days after treatment 77.6% and 80.5% of the subjects in the tablet and capsule group, respectively, were free of Candida spp., with similar rates at 6 to 8 weeks after treatment in the tablet group (78.1%) and slightly lower in the capsule group (74.6%). Mycological cure rates were similar for both treatment groups (77.6% and 81.0% at 10-14 days after treatment and 81.1% and 77.5% at 6 to 8 weeks after treatment for the tablet and capsule group, respectively) (table 4).

Table 4: Response rates for mycological cure (ITT population)

	- Tablets - N=192 n (%)	- Ovules - N=185 n (%)	- Tablets - N=192 n (%)	- Ovules - N=185 n (%)
	Visit 2		Visit 3	
Number of subjects with available data	192	184	185	178
Number of responders (n (%))	149 (77.6%)	149 (81.0%)	150 (81.1%)	138 (77.5%)
95% CI	(71.4%, 83.8%)	(75.0%, 86.9%)	(75.2%, 87.0%)	(71.1%, 83.9%)
Ovules-tablets (95% CI)	3.4% (-9.9%, 16.6%)		-3.6% (-17.0%, 9.9%)	

CI = confidence interval

IV.4 Clinical safety

Phase III non-inferiority study

All subjects, except for 2 subjects in the capsule group (withdrawn consent) received a single dose of either the clotrimazole tablet (228 subjects) or the capsule (235 subjects). For 7 subjects (capsule group n=5 and tablet group n=2) no information on study drug administration was available due to loss to follow-up prior to visit 2.

Both clotrimazole formulations were well tolerated. There was only one adverse event (AE), with the capsule formulation, which was considered drug-related (vulvovaginal discomfort of mild intensity, which started 4 days after application of the capsule). Overall 35 subjects (7.6%) experienced AEs after drug administration. The incidence was comparable for both treatment groups. Most AEs were of mild to moderate intensity. There were no serious AEs and five subjects discontinued the study due to AEs: 4 subjects in the tablet group (mild trichomoniasis, vaginal myoplasmatic infection, gluteal furuncle, acute bronchitis) and 1 subject in the capsule group (moderate angina tonsillaris).

Table 5: Overview of adverse events (Safety population)

	- Tablets - N=228	- Ovules - N=235	- Overall - N=463
Number of subjects with any adverse events	18 (7.9%)	17 (7.2%)	35 (7.6%)
Number of subjects with drug related adverse events	-	1 (0.4%)	1 (0.2%)
Number of subjects with severe adverse events of severe intensity	-	1 (0.4%)	1 (0.2%)
Number of subjects with serious adverse events	-	-	-
Number of subjects discontinued due to an adverse event	4 (1.8%)	1 (0.4%)	5 (1.1%)

The most frequently reported AE was abdominal pain (tablet group 2.2%, capsule group 1.3%). Abdominal pain occurred in most subjects within 1 week after drug application and mainly resolved on the same day. The intensity was mild except for 1 subject with moderate abdominal pain (tablet group). Two subjects in the tablet group reported a mild vaginal bleeding, which was considered as not drug-related by the investigator (table 6).

Table 6: Summary of treatment emergent adverse events reported overall by more than one subject (Safety population)

System organ class	Preferred term	- Tablets - N=228 x (y/ z%)	- Ovules - N=235 x (y/ z%)	- Overall - N=463 x (y/ z%)
Gastrointestinal disorders	Abdominal pain	6 (5, 2.2%)	3 (3, 1.3%)	9 (8, 1.7%)
	Nausea	1 (1, 0.4%)	1 (1, 0.4%)	2 (2, 0.4%)
Nervous system disorders	Headache	-	4 (4, 1.7%)	4 (4, 0.9%)
Psychiatric disorders	Insomnia	-	3 (2, 0.9%)	3 (2, 0.4%)
Reproductive system and breast disorders	Vaginal haemorrhage	3 (2, 0.9%)	-	3 (2, 0.4%)
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	1 (1, 0.4%)	2 (2, 0.9%)	3 (3, 0.6%)

x (y, z%): x = number of AE, y = number of subjects with particular AE (subjects were counted only once for each system organ class and preferred term, z = percentage of subjects with particular AE (refer to the number of subjects in safety population)

IV.5 Discussion on the clinical aspects

Study design

The submitted phase III study aimed to evaluate efficacy and safety of the Canesten single-dose 500 mg soft capsule in comparison to the approved Canesten 500 mg tablet in the treatment of vaginal candidiasis. The objectives and endpoints of the study are adequate. The endpoints are clinically relevant and similar endpoints have been used in previous studies investigating the efficacy of antimycotics in the treatment of vulvovaginal candidiasis. However, the study had the following limitations:

- Lack of a placebo-arm

Considering the self-limiting nature of vulvovaginal candidiasis and the relatively large clinical cure rate observed in the placebo group in the study of Bro et al. (1990), inclusion of a placebo-arm would have been preferred to ensure assay sensitivity of the study.

- Single-blind design

The single-blind design is another important limitation of the study, although it is understood given the different formulations. The primary endpoint was a composite measure, including mycological evaluation and clinical evaluation as rated by both investigators and subjects themselves. Since the subjects were not blind to the study medication, this could have impacted on the outcome of the study. Efficacy of the vaginal capsules was, however, also analysed for mycological cure and clinical cure (both signs as reported by the investigator and symptoms as reported by subjects) separately as part of the secondary objectives.

- Non-inferiority margin

The chosen non-inferiority margin of 15% is considered rather wide for comparing different formulations of the same active substance in the same quantitative composition. In addition, it is not agreed that non-inferiority can be concluded when the lower limit of the 95% CI for the responder rate of the capsule was larger than the observed response rate of the tablet minus 15%. Non-inferiority can only be concluded if the lower end of the 95% CI of the treatment difference is entirely to the right of the set non-inferiority margin (-15%) in accordance with EU guidance laid down in the 'Points to consider on switching between superiority and non-inferiority' (CPMP/EWP/482/99).

Study results

The observed drop-out rate of 25.2% was larger than anticipated (20%). Demographics and baseline characteristics of the final study population were largely similar for both treatment groups.

The new formulation appears to be non-inferior to the approved tablet formulation with regard to the primary endpoint (both mycological and clinical cure) in both the PP and ITT population, even in case a more conservative non-inferiority margin of 10% would have been used. In addition, responder rates were numerically higher in the capsule group compared to the tablet group. This was further strengthened by consistency in findings across secondary endpoints (mycological cure, resolution of symptoms, as determined by subjects themselves, and resolution of signs, as determined by investigators).

These findings suggest little or no relevant impact of the fact that subjects were not blind to the received study medication on the results regarding the primary endpoint.
Numerical superiority of the soft capsule formulation was not maintained at long-term follow-up (6-8 weeks after treatment) and the lower limit of the 95% CI of the treatment difference exceeded -15%, although the differences in treatment response rates were relatively small. The reasons for this apparent lower long-term efficacy compared to the tablet formulation are unknown.
Both formulations were well tolerated and no relevant differences in safety profiles between the treatment groups were observed.

In view of the uncertainties on assay sensitivity of the study, because of the lack of a placebo-arm, the MAH was asked to provide data to substantiate assay sensitivity of the non-inferiority study.

Literature data

The MAH submitted two publications of prospective, randomized, double-blind trials comparing efficacy and safety of a single dose of 500 mg clotrimazole (tablet) with placebo; studies by Hughes et al., 1984[1] and Bro et al., 1990[2].

Bro et al. reported a large clinical cure rate in the placebo group one week after treatment. In contrast, in the study of Hughes et al. there was no clinical cure at all in the placebo group one week after treatment. It was however noted that the study by Bro et al. showed serious limitations in study design (unknown concealment of allocation, 59% dropouts after randomization) and therefore, the large placebo-effect might be a result of these limitations rather than a true placebo-effect. Because these two studies seem to be the only published ones comparing the reference product with placebo, no conclusions can be drawn on assay sensitivity from the literature.

Conclusion

Taken altogether, it is not to be expected that the soft capsule is less effective or safe than the tablet based on the provided study data. Canesten gyno 500 mg vaginal tablets has been used for many years, and the active moiety has an accepted benefit/risk balance. Therefore, despite the limitations in the design of the non-inferiority study, Canesten Gyno 500 mg vaginal capsules is approvable as a line extension to the vaginal tablets. Non-inferiority is sufficiently demonstrated.

[1] Hughes D, Kriedman T. Treatment of vulvovaginal candidiasis with a 500mg vaginal tablet of clotrimazole. Clin Ther 1984:6(5):662–8.
[2] Bro F. Single-Dose 500-mg clotrimazole Vaginal Tablets Compared with Placebo in the Treatment of Candida Vaginitis. J Fam Pract 1990;31:148–52.

IV.6 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 Canesten Gyno.

Summary of safety concerns	
Important identified risks	Hypersensitivity reaction
Important potential risks	Risk of exposure of foetus during the first trimester of pregnancy Risk of exposure of neonate during lactation Risk of misdiagnosis Development of resistance Risk of accidental ingestion Risk of environmental toxicity Drug interaction with tacrolimus/sirolimus Drug interaction with latex condoms/diaphragms
Important missing information	None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

V. USER CONSULTATION

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. The test consisted of a pilot test with 5 participants, followed by two test rounds with ten participants each. The questionnaire consisted of 12 specific and 2 general questions. The questions address the key issues regarding safe and effective use of the medicine. Both rounds of testing showed that more than 90% of the participants were able to find the requested information, and of those, more than 90% were able to understand the information that was found and would act appropriately.
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

Canesten Gyno 1 soft capsule, 500 mg vaginal capsules has a proven chemical-pharmaceutical quality and is an approvable line extension to Canesten gyno 1 tablet, 500 mg vaginal tablets. This is a well-known medicinal product with an established favourable efficacy and safety profile.

In the Board meeting of 14 May 2014, the application was discussed. The quality dossier and design of the non-inferiority study were considered. The lack of a placebo arm and resulting assay sensitivity issue were evaluated. Based on the data presented in the dossier, the Board was unable to draw firm conclusions on the efficacy of the capsule compared to the tablet. The MAH was therefore asked to further substantiate non-inferiority. Having assessed the responses of the MAH, the Board concluded that the capsule formulation is not expected to be less effective or safe than the tablet. No statistically/clinically significant differences were observed between products.

Based on the totality of data, non-inferiority is demonstrated. Canesten Gyno 1 soft capsule, 500 mg was authorised in the Netherlands on 11 February 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the address of the Qualified Person Responsible for Pharmacovigilance (QPPV).	IA	27-11-2013	27-12-2013	Approval	N
Change in the QPPV and Pharmacovigilance System Summary (PSS).	IA	14-4-2015	14-5-2015	Approval	N
Change in the specification parameters and/or limits of an excipient.	IB	11-6-2015	11-7-2015	Approval	N
Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance. Change to comply with Ph.Eur. or with a national pharmacopoeia.	IA/G	29-10-2015	28-11-2015	Approval	N
Change in the mock-up.	--	10-12-2015	9-5-2016	Approval	N