

**CANESTEN COMBI 500MG SOFT GEL PESSARY & 2%
CREAM**

(Clotrimazole)

PL 00010/0636

UKPAR

TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 14
Steps taken after authorisation – summary	Page 15
Summary of Product Characteristics	Page 16
Product Information Leaflet	Page 20
Labelling	Page 22
Annex 1	Page 24

CANESTEN COMBI 500MG SOFT GEL PESSARY & 2% CREAM

PL 00010/0636

LAY SUMMARY

The MHRA granted Bayer plc a Marketing Authorisation (licence) for the medicinal product Canesten Combi 500mg Soft Gel Pessary & 2% Cream on 05 September 2011. This product is a prescription-only medicine (POM).

Canesten Combi 500mg Soft Gel Pessary & 2% Cream is a full course of treatment for vaginal thrush (candidiasis) because it treats both the internal cause and external symptoms. It is also used to treat other vaginal infections such as Trichomoniasis.

The active substance in Canesten Combi 500mg Soft Gel Pessary & 2% Cream is clotrimazole. Clotrimazole belongs to a group of medicines called azoles and is an antifungal agent which fights the cause of infections such as vaginal thrush.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Canesten Combi 500mg Soft Gel Pessary & 2% Cream outweigh the risks, hence a Marketing Authorisation has been granted.

CANESTEN COMBI 500MG SOFT GEL PESSARY & 2% CREAM

PL 00010/0636

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Non-clinical assessment	Page 8
Clinical assessment	Page 9
Overall conclusions and risk benefit assessment	Page 13

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bayer plc, a Marketing Authorisation for the medicinal product Canesten Combi 500mg Soft Gel Pessary & 2% Cream (PL 00010/0636) on 05 September 2011. This product is a prescription-only medicine (POM) and is indicated for the treatment of candidal vaginitis and mixed vaginal infections where *Trichomonas* is present or suspected.

This is a standard abridged application submitted under Article 10(3) of Directive 2001/83/EC as amended, as a hybrid application. The reference medicinal product for this application is Canesten Combi Pessary & Cream (PL 00010/0300) which was originally granted a licence to Bayer plc, UK.

Canesten Combi 500mg Soft Gel Pessary & 2% Cream contains the active ingredient clotrimazole. Clotrimazole is an imidazole derivative with a broad spectrum of antimycotic activity which includes dermatophytes, yeasts, and moulds. Clotrimazole acts by inhibition of the ergosterol synthesis leading to structural and functional impairment of the fungal membrane. The mode of action of clotrimazole is fungistatic or fungicidal depending on the concentration of clotrimazole. Resistance to clotrimazole is extremely rare in vaginal isolates and despite its widespread use over decades no overt change of the susceptibility of relevant fungi has been detected. Clotrimazole is also active against gram-positive bacteria and *Trichomonas vaginalis*.

No new non-clinical studies were submitted with this application, which is acceptable given that this is a hybrid application with an originator product that has been licensed for over 10 years.

The clinical study was conducted in accordance with Good Clinical Practice (GCP).

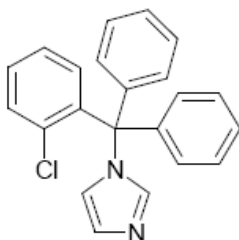
No new or unexpected safety concerns were raised during the assessment of this application and it was, therefore, judged that the benefits of using Canesten Combi 500mg Soft Gel & 2% Cream outweigh the risks; hence a Marketing Authorisation has been granted.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Clotrimazole
Chemical names: 1-(2-chloro- α,α -diphenyl-benzyl)imidazole
1-(*o*-chloro- α,α -diphenyl-benzyl)imidazole
1-(2-chlorotriptyl)imidazole
1-[(2-chlorophenyl)-diphenylmethyl]1*H*-imidazole

Structure:



Molecular formula: $C_{22}H_{17}ClN_2$
Molecular weight: 344.8
Appearance: Clotrimazole is a white to slightly yellowish fine crystalline powder which is practically insoluble in water, freely soluble in ethanol and chloroform, sparingly soluble in ether.

Clotrimazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance clotrimazole are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

MEDICINAL PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely:

Soft gel pessary

White soft paraffin, liquid paraffin, gelatin, glycerol, water, titanium dioxide (E171), quinoline yellow (E104), sunset yellow (E110), lecithin and medium-chain triglycerides.

Cream

Sorbitan stearate, polysorbate 60, cetyl palmitate, cetostearyl alcohol, octyldodecanol, benzyl alcohol and purified water.

Appropriate justification for the inclusion of each excipient has been provided.

With the exception of lecithin, sunset yellow and quinoline yellow, all excipients used comply with their respective European Pharmacopoeia monograph. Lecithin is compliant with National Formulary-US pharmacopoeia (USP). Quinoline yellow and sunset yellow are controlled to suitable in-house specifications and are in compliance with current EU

directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided certificates of suitability from the European Directorate for the Quality of Medicines (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical development

The aim of the development programme was to formulate a soft gelatin capsule containing 500 mg of clotrimazole in a stable suspension and a safe, efficacious, stable cream containing 2 % clotrimazole.

Suitable pharmaceutical development data have been provided for this application.

The physico-chemical properties of the Canesten cream contained within this combination product have been compared with the reference product. These demonstrate that the proposed product can be considered equivalent to the Canesten cream of the innovator product (PL 00010/0300).

Manufacture

A description and flow-chart of the manufacturing methods has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated and have shown satisfactory results.

Finished product specification

The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The finished product is packaged into:

Soft gel pessary

Blisters consisting of formed clear triplex laminate film polyvinylchloride/polyvinylidene chloride/polyvinylchloride (total PVC 250µm; PVdC 120g/m²) sealed with 20 µm hard tempered aluminium lidding foil. The blister and an applicator are enclosed in a cardboard carton.

Cream

Aluminium tubes with internal lacquer coating, latex stopper with high density polyethylene (HDPE) screw top in pack sizes of 10 g.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability

Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with the storage conditions “This product should be stored in the original carton in a dry place in order to protect it from moisture. Do not store above 30°C”.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SmPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form

The MAA form is satisfactory.

Expert Report

A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

It is recommended that a marketing authorisation is granted for this application.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

The pharmacological, pharmacokinetic and toxicological properties of clotrimazole are well-known. As this active substance is well-known, no further studies are required and the applicant has provided none. An overview based on a literature review is, thus, appropriate.

NON-CLINICAL EXPERT REPORT

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for substitution with products that are already currently being marketed, there is not anticipated to be any increase in environmental burden.

CONCLUSION

It is recommended that a marketing authorisation is granted for this application.

CLINICAL ASSESSMENT

Pharmacokinetics

No new pharmacokinetic data have been submitted and none are required. As the product is a locally acting medicine and previous studies have shown that systemic concentrations are negligible, this is acceptable.

Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for this application.

Efficacy

The following therapeutic equivalence (non-inferiority) study was submitted to support this application:

An investigator-blind, two-arm, multicentre, randomised clinical trial to compare the safety and efficacy of the test product Clotrimazole Soft Gel Pessary (ovule) versus the reference product Clotrimazole 500mg vaginal tablets (Bayer plc, UK) in women with vulvovaginal mycosis.

All subjects were randomised to one of the two treatment groups. The study was investigator-blind, i.e the packages distributed to the subjects could not be distinguished by the investigator. At Visit 1, all subjects were instructed to apply the study medication (one soft vaginal capsule or vaginal tablet) with an applicator prior to laying down for sleep. Follow-up examinations were conducted at Visit 2 (2 weeks, 10-15 days post dose) and Visit 3 (6-8 weeks, 42-60 days post dose).

The clinical symptoms (itching, burning, irritation, discharge, and dysuria), signs (vaginal and vulval oedema, erythema, and excoriation) and mycological tests (KOH and yeast culture preparation) were measured at baseline and the follow-up visits. The clinical signs were evaluated by the investigators on a 4-point scale (0=not present to 3=severe) at baseline and at follow up visits. In addition, the patients subjectively rated the symptoms of vaginitis (itching, burning/irritation, discharge and dysuria) on a 4-point scale, and kept diaries between visits 1 and 2 to record symptoms and adverse events.

The primary efficacy objective was the overall response rate at Visit 2, comprising of the clinical cure and mycological cure (main analysis based on the Per-Protocol population). Non-inferiority of the soft vaginal capsule formulation was concluded when the lower 95% confidence interval was greater than the observed response rate of the vaginal tablet -15%. Secondary efficacy parameters (main analyses based on the ITT population) were the overall response at Visit 3 and the clinical and mycological cure rates at Visits 2 and 3, which were also analysed for non-inferiority of the soft vaginal capsule formulation. The responder rate for cure of clinical symptoms (rated by patients) was defined as absence of the symptoms itching and burning/irritation and no more than mild discharge or dysuria and no worsening since visit 1. Cure with regard to signs of vaginitis (rated by the investigators) was defined as no more than mild vaginal and vulval signs and no worsening since visit 1.

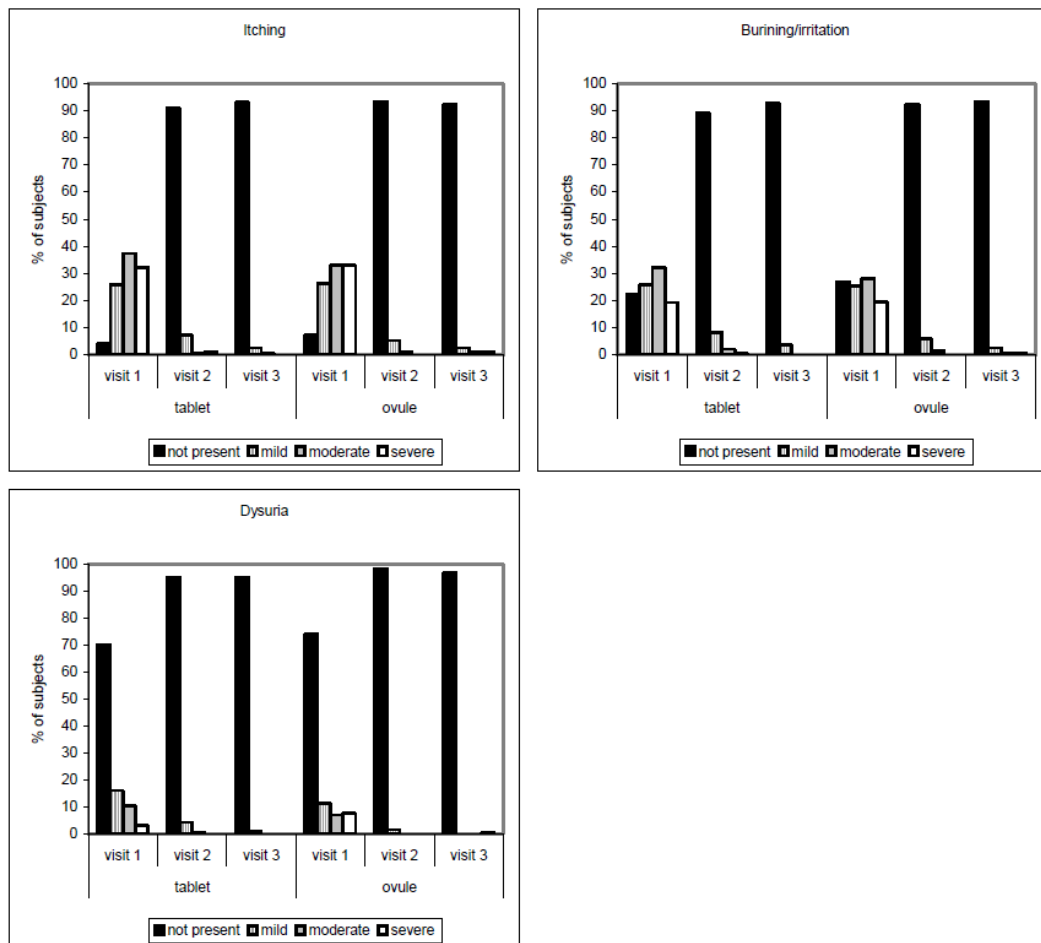
All subjects who completed the treatment and at least Visit 2, had a positive mycological test for *Candida spp.* at baseline and had no major protocol violations were included in the Per-Protocol (PP) population. All subjects, who completed treatment and at least Visit 2,

and had a positive *Candida* test at baseline, were included in the Intention-To-Treat (ITT) population and all subjects, who received the study medication, in the safety population

The overall response at Visit 2 and Visit 3 is presented below:

Visit 2	Vaginal tablets, n (%)	Soft vaginal capsules, n (%)
PP population:	n = 186	n = 180
Responder rate, n (%)	123 (66.1%)	132 (73.3%)
95% CI	59.2%, 73.2%	66.6%, 80.1%
Difference capsules-tablets (95% CI)	7.2% (-7.3%, 21.7%)	
ITT population:	n = 192	n = 185
Responder rate, n (%)	126 (65.6%)	134 (72.4%)
95% CI	58.6%, 72.6%	65.7%, 79.1%
Difference capsules-tablets (95% CI)	7.2% (-7.3%, 21.7%)	
Visit 3	Vaginal tablets, n (%)	Soft vaginal capsules, n (%)
PP population:	n = 169	n = 169
Responder rate, n (%)	128 (75.7%)	124 (73.4%)
95% CI	69.0%, 82.5%	66.4%, 80.3%
Difference capsules-tablets (95% CI)	-2.4% (-17.0%, 12.2%)	
ITT population:	n = 184	n = 178
Responder rate, n (%)	138 (75.0%)	129 (72.5%)
95% CI	68.5%, 81.5%	65.6%, 79.3%
Difference capsules-tablets (95% CI)	-2.5% (-16.7%, 11.7%)	

The individual clinical symptoms of vaginitis in the ITT population at each visit are presented below:



In the majority of patients, clinical signs and symptoms had resolved by Visit 2, and culture was negative in most patients independent of treatment. Cure of clinical symptoms was achieved by Week 2 in 84.4% and 88.1%, and cure of clinical signs of vaginitis in 96.9% and 98.4% of women using vaginal tablet and soft vaginal capsule, respectively. The cure rate of clinical symptoms increased in both groups until the second follow-up visit, while cure rate of clinical signs remained stable until Weeks 6-8. At 2 weeks after treatment, cultures were negative in 77.6% and 81.0% of women using vaginal tablet and soft vaginal capsule, respectively, and no overt change occurred until Week 6-8 after application (81.1% tablet versus 77.5% capsule). The differences between treatments were neither statistically nor clinically significant for any of the efficacy outcomes.

Response rates for clinical signs and symptoms, and mycological cure, are presented below for the ITT population:

	Vaginal tablets n = 192 (%)	Soft vaginal capsules n = 185 (%)	Vaginal tablets n = 192 (%)	Soft vaginal capsules n = 185 (%)
Clinical symptoms	Visit 2		Visit 3	
Subjects with available data (n)	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%
Capsules-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%
Capsules-tablets (95% CI)	1.5% (-6.6%, 9.6%)		-3.9% (-12.3%, 4.5%)	
Mycological cure	Visit 2		Visit 3	
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%
Capsules-tablets (95% CI)	3.4% (-9.9%, 16.6%)		-3.6% (-17.0%, 9.9%)	

The lower limit of the 95% CI for the responder rate of the soft vaginal capsule was larger than the observed responder rate of the vaginal tablet minus 15% at Visit 2 (as well as Visit 3) and, therefore, non-inferiority of the soft vaginal capsule compared to the vaginal tablet formulation has been proven. The observed difference between groups was small and not statistically significant (p=0.33). The ITT analysis confirmed the non-inferiority of the soft vaginal capsule formulation with regard to the primary as well as the secondary efficacy outcomes.

In conclusion, a single dose of Clotrimazole Soft Gel Pessary was non-inferior to a single dose of Clotrimazole 500 mg vaginal tablet in terms of overall response, defined as clinical and mycological cure, 14 days after treatment. It was also non-inferior to Clotrimazole vaginal tablet in terms of overall response at 6-8 weeks after treatment. Differences between the two treatment groups in clinical cure at 2 weeks and at 6 to 8 weeks after treatment were without clinical/statistical significance, and the soft gel pessary formulation proved to be non-inferior to the tablet formulation. Mycological cure rates were similar for both treatment groups at both 2 weeks and 6 to 8 weeks after treatment. At both visits, the soft gel pessary formulation proved to be non-inferior to the tablet formulation.

Safety

With the exception of the data generated during the therapeutic equivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the therapeutic equivalence study data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labels are acceptable. The PIL is consistent with the SmPC and in-line current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan

The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for this product.

Conclusion

There are no objections to the approval of this product from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Canesten Combi 500mg Soft Gel Pessary & 2% Cream are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY

Non-inferiority of Canesten soft gel pessary in comparison to Clotrimazole 500mg vaginal tablets (Bayer plc, UK) has been established, with no statistically/clinically significant differences observed between products.

No clinical studies have been conducted to support Canesten Cream contained within this combination product. Essential similarity with the originator product is based on the comparative quality attributes of the product. The applicant refers to clarification provided from the Co-ordination Group for Mutual Recognition and Decentralised Procedures - human (CMD(h)) [CMD (h) minutes from meeting held on 20 and 21 April 2009], this application is made under Article 10.3 (hybrid) of Directive 2001/83/EC, which states that bioequivalence cannot be demonstrated through bioavailability studies for products for local use intended to act without systemic absorption.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The therapeutic equivalence study supports the claim that the applicant's product is non-inferior to the reference product. Extensive clinical experience with clotrimazole is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

CANESTEN COMBI 500MG SOFT GEL PESSARY & 2% CREAM

PL 00010/0636

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the marketing authorisation application on 12 July 2010.
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 09 August 2010.
- 3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 08 November 2010 and the quality dossier on 08 November 2010 and 13 July 2011.
- 4 The applicant responded to the MHRA's requests, providing further information on the clinical dossier on 28 April 2011 and the quality dossier on 28 April 2011 and 08 August 2011.
- 5 The application was determined on 05 September 2011.

CANESTEN COMBI 500MG SOFT GEL PESSARY & 2 % CREAM

PL 00010/0636

STEPS TAKEN AFTER ASSESSMENT

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The update has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
22 February 2012	Type 1B	To update sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration) and 4.3 (Contraindications) of the SmPC in line with the reference products, Canesten Combi 500mg Pessary and 2% Cream (PL 00010/0258 and PL 00010/0077). The Patient Information Leaflet (PIL) has not been updated as no amendments were necessary.	Granted 28 February 2012

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Canesten Combi 500mg Soft Gel Pessary & 2% Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Canesten 500mg Soft Gel Pessary contains Clotrimazole 500mg.

Canesten Combi 2% Cream contains Clotrimazole 2% w/w.

Excipient(s):

Cream: cetostearyl alcohol 10% w/w

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal capsule, soft

Yellow teardrop-shaped soft capsule

Cream

White cream

4 CLINICAL PARTICULARS

4.1 *Therapeutic indications*

Canesten 500mg Soft Gel Pessary is indicated for the treatment of candidal vaginitis and mixed vaginal infections where *Trichomonas* is present or suspected. This product is not recommended as sole treatment for pure *Trichomoniasis* except in cases where systemic therapy is contra-indicated.

The cream is indicated for the treatment of candidal vulvitis. It should be used as an adjunct to treatment of candidal vaginitis.

4.2 *Posology and method of administration*

Adults:

One 500mg soft gel pessary should be inserted at night. Using the applicator provided, the soft gel pessary should be inserted as high as possible into the vagina. This is best achieved when lying back with legs bent up. A second treatment may be carried out if necessary.

Generally:

Treatment during the menstrual period should not be performed due to the risk of the soft gel pessary being washed out by the menstrual flow. The treatment should be finished before the onset of menstruation.

Do not use tampons, intravaginal douches, spermicides or other vaginal products while using this product.

The cream should be thinly applied to the vulva and surrounding area, two or three times daily and rubbed in gently.

Treatment with the cream should be continued until symptoms of the infection disappear. However, if after concomitant treatment of the vaginitis, the symptoms do not improve within seven days, the patient should consult a physician.

Children: Not recommended for children under 16 as the product is used with an applicator.

4.3 *Contraindications*

Hypersensitivity to clotrimazole or any ingredient in this medicine.

Hypersensitivity to cetostearyl alcohol.

Do not use to treat nail or scalp infections.

4.4 *Special warnings and precautions for use*

Patients should be advised to consult their physician if the symptoms have not been relieved within one week of using Canesten 500mg Soft Gel Pessary. Canesten 500mg Soft Gel Pessary can be used again if the candidal infection returns after 7 days. However, if the candidal infection recurs more than twice within six months, patients should be advised to consult their physician.

4.5 *Interaction with other medicinal products and other forms of interaction*

Concomitant medication with vaginal clotrimazole and oral tacrolimus (FK-506; immunosuppressant) might lead to increased tacrolimus plasma levels. Patients should thus be closely monitored for signs and symptoms of tacrolimus overdose, if necessary by determination of the respective plasma levels.

Laboratory tests have suggested that, when used together, this product may cause damage to latex contraceptives. Consequently the effectiveness of such contraceptives may be reduced. Patients should be advised to use alternative precautions for at least five days after using this product.

4.6 *Pregnancy and lactation*

Data on a large number of exposed pregnancies indicate no adverse effects of Clotrimazole on pregnancy or on the health of the foetus/newborn child. To date, no relevant epidemiological data are available.

Clotrimazole can be used during pregnancy, but only under the supervision of a physician or midwife.

During pregnancy the soft gel pessary should be inserted without using an applicator.

4.7 *Effects on ability to drive and use machines*

Not applicable.

4.8 *Undesirable effects*

As the listed undesirable effects are based on spontaneous reports, assigning accurate frequency of occurrence for each is not possible

Immune system disorders:

allergic reaction (syncope, hypotension, dyspnea, urticaria, pruritus)

Canesten Soft Gel Pessary

Reproductive system and breast disorders:

genital peeling, pruritus, rash, oedema, discomfort, burning, irritation, pelvic pain

Gastrointestinal disorders:

abdominal pain

Canesten Cream

Skin and subcutaneous tissue disorders: blisters, discomfort/pain, oedema, irritation, peeling/exfoliation, pruritus, rash, stinging/burning

4.9 *Overdose*

In the event of accidental oral ingestion, routine measures such as gastric lavage should be performed only if clinical symptoms of overdose become apparent (e.g. dizziness, nausea or vomiting). It should be carried out only if the airway can be protected adequately.

5 PHARMACOLOGICAL PROPERTIES

5.1 *Pharmacodynamic properties*

ATC Code: G01A F02 Gynaecological antiinfectives and antiseptics – imidazole derivatives

Clotrimazole is an imidazole derivative with a broad spectrum of antimycotic activity.

Mechanism of Action

Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the cytoplasmic membrane.

Pharmacodynamic Effects

Clotrimazole has a broad antimycotic spectrum of action in vitro and in vivo, which includes dermatophytes, yeasts, moulds, etc.

Under appropriate test conditions, the MIC values for these types of fungi are in the region of less than 0.062 – 8 µg/ml substrate. The mode of action of clotrimazole is fungistatic or fungicidal depending on the concentration of clotrimazole at the site of infection. In-vitro activity is limited to proliferating fungal elements; fungal spores are only slightly sensitive.

In addition to its antimycotic action, clotrimazole also acts on *Trichomonas vaginalis*, gram-positive microorganisms (Streptococci/Staphylococci) and gram-negative microorganisms (*Bacteroides/Gardnerella vaginalis*). It has no effect on lactobacilli.

In vitro, clotrimazole inhibits the multiplication of *Corynebacteria* and gram-positive cocci – with the exception of *Enterococci* – in concentrations of 0.5 – 10 µg/ml substrate and exerts a trichomonacidal action at 100 µg/ml.

Primarily resistant variants of sensitive fungal species are very rare; the development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions.

5.2 *Pharmacokinetic properties*

Pharmacokinetic investigations after vaginal application have shown that only a small amount of clotrimazole (3 – 10%) is absorbed. Due to the rapid hepatic metabolism of absorbed clotrimazole into pharmacologically inactive metabolites the resulting peak plasma concentrations of clotrimazole after vaginal application of a 500mg dose were less than 10 ng/ml, reflecting that clotrimazole applied intravaginally does not lead to measurable systemic effects or side effects.

Pharmacokinetic investigations after dermal application have shown that clotrimazole is practically not absorbed from the intact or inflamed skin into the human blood circulation. The resulting peak serum concentrations of clotrimazole were below the detection limit of 0.001 µg/ml, reflecting that clotrimazole applied topically does not lead to measurable systemic effects or side effects.

5.3 *Preclinical safety data*

There are no pre-clinical data of relevance to the prescriber which are additional to the information included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 *List of excipients*

The soft gel pessary contains:

White soft paraffin
Liquid paraffin
Gelatin
Glycerol
Water
Titanium dioxide (E171)
Quinoline yellow (E104)
Sunset yellow (E110)
Lecithin
Medium-chain triglycerides.

The cream contains:

Sorbitan stearate
Polysorbate 60
Cetyl palmitate
Cetostearyl alcohol
Octyldodecanol

Benzyl alcohol
Purified Water

6.2 *Incompatibilities*
Not applicable.

6.3 *Shelf life*
3 years

6.4 *Special precautions for storage*
This product should be stored in the original carton in a dry place in order to protect it from moisture.
Do not store above 30°C.

6.5 *Nature and contents of container*
Each soft gel pessary is packed into a blister consisting of formed clear triplex laminate film PVC/PVdC/PVC (Total PVC 250µm; PVdC 120g/m²) sealed with 20 µm hard tempered aluminium lidding foil and is supplied with an applicator.

The cream is filled into Aluminium tubes (10g) with internal lacquer coating, latex stopper and HDPE screw top.

6.6 *Special precautions for disposal*
No special requirements

7 **MARKETING AUTHORISATION HOLDER**

Bayer plc
Bayer House
Strawberry Hill
Newbury, Berkshire
RG14 1JA
United Kingdom

Trading as Bayer plc, Consumer Care Division.

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00010/0636

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
05/09/2011

10 **DATE OF REVISION OF THE TEXT**
05/09/2011

Module 3

PATIENT INFORMATION LEAFLET

Canesten®



COMBI

500mg Soft Gel Pessary & 2% Cream

Clotrimazole

Read all of this leaflet carefully because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not give it to anyone else under any circumstances.
- If you have any unusual effects after using this product, tell your doctor.

IN THIS LEAFLET

1. What is Canesten Combi and what is it used for?
2. Before you use Canesten Combi
3. How to use Canesten Combi
4. Possible side effects
5. How to store Canesten Combi
6. Further information

1. WHAT IS CANESTEN® COMBI AND WHAT IS IT USED FOR?

Canesten Combi 500mg Soft Gel Pessary & 2% Cream is a full course of treatment for vaginal thrush (candidiasis) because it treats both the internal cause and external symptoms. It is also used to treat other vaginal infections such as Trichomoniasis.

Some women suffer from recurrent attacks of thrush. To reduce the frequency of these attacks, the sexual partner's penis can be treated with this cream to prevent re-infection, even if they have no symptoms of thrush.

The active substance in Canesten 500mg Soft Gel Pessary & 2% Cream is clotrimazole. Clotrimazole belongs to a group of medicines called azoles and is an antifungal agent which fights the cause of infections such as vaginal thrush.

2. BEFORE YOU USE CANESTEN® COMBI

Do not use Canesten® Combi 500mg Soft Gel Pessary & 2% Cream:

- If you are allergic (hypersensitive) to clotrimazole or any of the other ingredients, including cetostearyl alcohol, of Canesten Combi 500mg Soft Gel Pessary & 2% Cream (see Section 6. Further Information).

Important information about some of the ingredients:

The cream contains cetostearyl alcohol which may cause local skin irritation (e.g. rash, itching or redness).

Special precautions:

As with other creams and pessaries, this product may reduce the effectiveness of rubber contraceptives, such as condoms or diaphragms. Consequently, you should use alternative precautions for at least five days after using this product.

Do not use tampons, intravaginal douches, spermicides or other vaginal products while using this product.

Do not use this product during your period as it may be less effective.

Using other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Inform your doctor if you are taking tacrolimus (used to reduce the immune response to prevent rejection after an organ transplant).

Pregnancy:

If you are pregnant or trying for a baby, tell your doctor or midwife before using Canesten Combi 500mg Soft Gel Pessary & 2% Cream. If you have informed your doctor or midwife already, follow his/her instructions carefully.

To treat internal thrush, your doctor may recommend that you use the pessary without the help of an applicator.

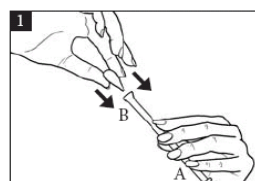
3. HOW TO USE CANESTEN® COMBI

The Soft Gel Pessary:

Unless directed otherwise by your doctor, the Soft Gel Pessary should be inserted as high as possible into the vagina, preferably before going to sleep at night for convenient and comfortable treatment.

Wash your hands before removing the foil from the blister pack and again afterwards when you have used the applicator.

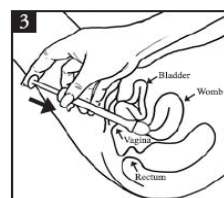
1. Remove the applicator from the packaging. Pull out the plunger A until it stops. Remove the pessary from the foil blister pack and place firmly into the applicator B.



2. Fix the Soft Gel Pessary firmly into the designated holder of the applicator B, by a light twist. The pessary fits tightly into the applicator.



3. Carefully put the applicator as deep as is comfortable into the vagina (this is easiest when lying on your back with your knees bent up). Holding the applicator in place, slowly press the plunger until it stops so that the pessary is deposited into the vagina.



4. Remove the applicator. Dispose of the applicator in a safe place, out of the reach of children. The applicator cannot be flushed down the toilet.

Since the pessary dissolves in the vagina, it may be helpful to wear a panty liner.

The Cream:

Women:

Before use, pierce the tube seal by inverting the cap over the end of the tube and press.

To treat the itching and soreness of the vulva, the cream should be thinly and evenly applied to the area around the entrance of the vagina, 2 or 3 times a day and smoothed in gently. Treatment should be continued until the symptoms of the infection disappear.

The symptoms of thrush should disappear within three days of treatment. If no improvement is seen after seven days you must tell your doctor. If the infection returns after seven days you may use one further treatment, but if you have more than two infections within six months you should see your doctor.

Treating your sexual partner:

If your sexual partner is treated with this cream, the cream should be applied to the end of the penis 2 or 3 times a day for up to two weeks.

Canesten Combi 500mg Soft Gel Pessary & 2% Cream is not recommended for use in children under 16 years old.

The Soft Gel Pessary is for use in the vagina only.

The cream is for external use only:

Do not put the pessary or cream in your mouth or swallow them.

If the pessary or cream are swallowed accidentally, tell your doctor straight away or contact the Accident and Emergency Department of your nearest hospital.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Canesten Combi 500mg Soft Gel Pessary & 2% Cream can cause side effects, although not everybody gets them.

As with all medicines, some people may be allergic to the pessary or cream. If you are allergic, a reaction will occur soon after you have used the medicine. If you experience an allergic reaction or the redness, burning, pain, itching or swelling get worse, stop using this product and tell your doctor straight away or contact the Accident and Emergency Department of your nearest hospital. Signs of an allergic reaction may include:

- Rash.
- Swallowing or breathing problems.
- Swelling of your lips, face, throat or tongue.
- Weakness, feeling dizzy or faint.
- Nausea.

After you use the pessary you might experience:

- Itching, rash, swelling, discomfort, burning, irritation or vaginal peeling.
- Pain in the abdomen or pelvic area.

After you apply the cream you might experience:

- Itching, rash, blisters, burning, discomfort, swelling, irritation or peeling of skin.

If you experience any of the above effects or react badly to the pessary or cream in any other way not listed in this leaflet, tell your doctor immediately.

5. HOW TO STORE CANESTEN® COMBI

Keep out of the reach and sight of children.

This product should be stored in the original carton in a dry place in order to protect from moisture.

Do not store above 30°C.

Do not use the pessary or cream after the expiry date which is stated at one end of the carton, on the foil blister strip of the pessary and on the end of the tube of cream. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Canesten® Combi 500mg Soft Gel Pessary & 2% Cream contains:

Soft Gel Pessary:

- The active substance is clotrimazole at a strength of 500mg.

- The other ingredients are white soft paraffin, liquid paraffin, gelatin, glycerol, water, titanium dioxide (E171), quinoline yellow (E104), sunset yellow (E110), lecithin, medium-chain triglycerides.

Cream:

- The active substance is clotrimazole at a strength of 2% w/w.

- The other ingredients are benzyl alcohol, polysorbate 60, sorbitan stearate, cetyl palmitate, cetostearyl alcohol, octyldodecanol and purified water.

See Section 2 'Do not use' and 'Important information about some of the ingredients' for cetostearyl alcohol advice.

What Canesten® Combi 500mg Soft Gel Pessary & 2% Cream looks like and contents of the pack:

Canesten Combi 500mg Soft Gel Pessary & 2% Cream contains a full course of treatment, which consists of a single yellow teardrop-shaped soft vaginal capsule held inside a foil blister pack, one applicator for insertion of the pessary into the vagina and one 10g tube of white cream.

Marketing Authorisation Holder:

Bayer plc, Consumer Care Division
Bayer House, Strawberry Hill
Newbury, Berkshire RG14 1JA, UK.

Manufacturer: GP Grenzach Produktions GmbH,
79639 Grenzach-Wyhlen, Germany.

Remember: This medicine has been prescribed for you.

Do not give it to anyone else under any circumstances.

If you have any doubts about using Canesten® Combi 500mg Soft Gel Pessary & 2% Cream correctly, seek the advice of your doctor or pharmacist.

Further information about vaginal thrush:

Vaginal thrush (candidiasis) is a common infection that most women suffer from at some time in their lives and is not caused by lack of personal hygiene.

Thrush is caused by a yeast (fungus) called Candida which lives harmlessly in the vagina and other parts of the body, without you even noticing it. However, the natural balance that keeps Candida under control can be upset by many factors such as hormonal changes (menstruation, contraceptive pill, pregnancy, menopause), poor health, antibiotics, perfumed soaps, bath additives and tight clothing.

If the natural pH balance is altered, the level of yeast increases and can develop into a thrush infection causing any of the following symptoms: persistent burning and/or itching around the vagina and vulva, redness, swelling and soreness of the tissues of the vagina and vulva and a whitish, odourless discharge from the vagina. Not everybody who has thrush has all these symptoms; you may have only one of them.

How to avoid future recurrences:

- ✓ Wear cotton knickers and loose clothing.
- ✓ Wash daily.
- ✓ After going to the toilet, wipe yourself from the front to back as a thrush infection may be transferred from the bowel.
- ✓ Change your sanitary protection regularly.
- ✗ Try to avoid wearing tights, nylon knickers and close fitting jeans.
- ✗ Try to avoid washing with perfumed soaps or using vaginal deodorants.
- ✗ Do not wash or rub yourself hard with sponges or flannels and avoid hot baths with strong perfumed oils.

If you are still worried or have any questions about the symptoms or the treatment of thrush, do not hesitate to ask your doctor or pharmacist for advice.

For UK residents only: if you have any questions or would like more information, call our Canesten Advice Line on 0845 758 5030. Calls charged at local rate.

This leaflet was last revised in March 2011.

Canesten is a registered trademark of Bayer AG, Germany.

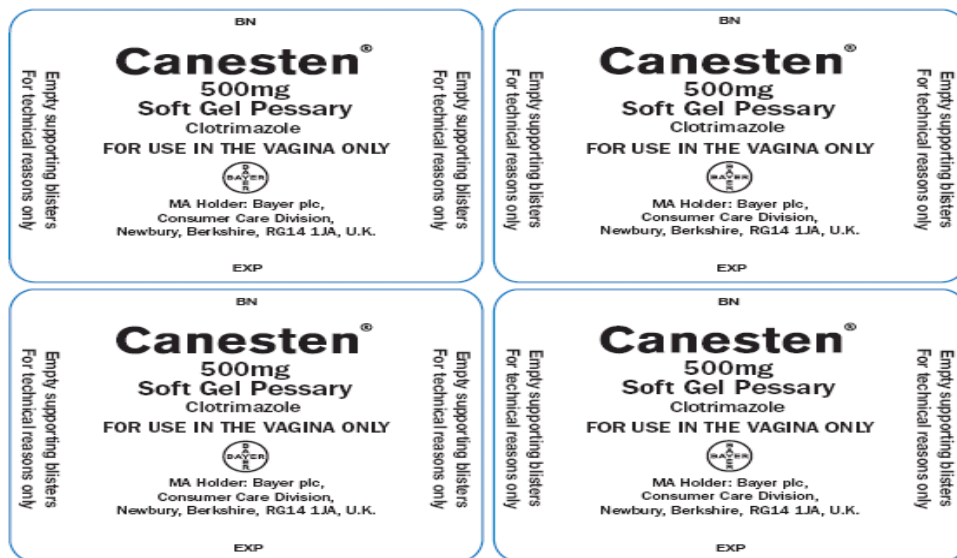
Bayer

Module 4 LABELLING

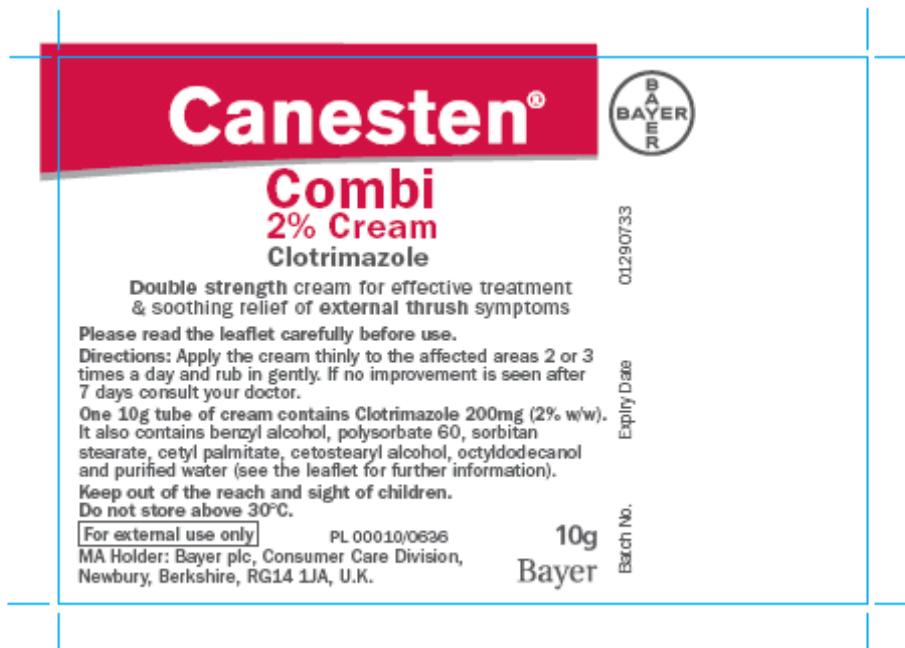
Carton:




Blister



Tube:



Canesten[®]



Combi
2% Cream
Clotrimazole

**Double strength cream for effective treatment
& soothing relief of external thrush symptoms**

Please read the leaflet carefully before use.

Directions: Apply the cream thinly to the affected areas 2 or 3 times a day and rub in gently. If no improvement is seen after 7 days consult your doctor.

One 10g tube of cream contains Clotrimazole 200mg (2% w/w). It also contains benzyl alcohol, polysorbate 60, sorbitan stearate, cetyl palmitate, cetostearyl alcohol, octyldodecanol and purified water (see the leaflet for further information).

Keep out of the reach and sight of children.
Do not store above 30°C.

10g
Bayer

01290733
Expiry Date

Batch No.

For external use only PL 00010/0636
MA Holder: Bayer plc, Consumer Care Division,
Newbury, Berkshire, RG14 1JA, U.K.

Annex 1

Reference:	PL 00010/0636-0004
Product:	Canesten Combi 500mg Soft Gel Pessary & 2% Cream
Marketing Authorisation Holder:	Bayer plc.
Active Ingredient(s):	Clotrimazole

Reason

To update sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration) and 4.3 (Contraindications) of the SmPC in line with the reference products, Canesten Combi 500mg Pessary and 2% Cream (PL 00010/0258 and PL 00010/0077). The Patient Information Leaflet (PIL) has not been updated as no amendments were necessary.

Evaluation

A satisfactory, updated SmPC was submitted in support of the variation application. The variation was approved on 28 February 2012 and the following updated SmPC has been incorporated into the Marketing Authorisation.

Conclusion

The proposed amendments to the SmPC are acceptable.

Summary of Product Characteristics – updated

The SmPC fragments updated for this variation are reproduced below:

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Canesten 500mg Soft Gel Pessary is indicated for the treatment of candidal vaginitis and mixed vaginal infections where *Trichomonas* is present or suspected. This product is not recommended as sole treatment for pure *Trichomoniasis* except in cases where systemic therapy is contra-indicated.

The cream is indicated for the treatment of candidal vulvitis. It should be used as an adjunct to treatment of candidal vaginitis. It can also be used for treatment of the sexual partner's penis to prevent re-infection.

4.2 Posology and method of administration

Adults:

One 500mg soft gel pessary should be inserted at night. Using the applicator provided, the soft gel pessary should be inserted as high as possible into the vagina. This is best achieved when lying back with legs bent up. A second treatment may be carried out if necessary.

Generally:

Treatment during the menstrual period should not be performed due to the risk of the soft gel pessary being washed out by the menstrual flow. The treatment should be finished before the onset of menstruation.

Do not use tampons, intravaginal douches, spermicides or other vaginal products while using this product.

The cream should be thinly applied to the vulva and surrounding area, two or three times daily and rubbed in gently.

Treatment with the cream should be continued until symptoms of the infection disappear. However, if after concomitant treatment of the vaginitis, the symptoms do not improve within seven days, the patient should consult a physician.

If the cream is being used for treatment of the sexual partner's penis it should be applied two or three times daily for up to two weeks.

Children:

Not recommended for children under 16 as the product is used with an applicator.

4.3 Contraindications

Hypersensitivity to clotrimazole or any ingredient in this medicine.

Hypersensitivity to cetostearyl alcohol.

Decision-Approved 28/02/2012.