CANESEN SOFT GEL PESSARY

(Clotrimazole)

PL 00010/0633

UKPAR

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CANESTEN SOFT GEL PESSARY

PL 00010/0633

LAY SUMMARY

The MHRA granted Bayer plc a Marketing Authorisation (licence) for the medicinal product Canesten Soft Gel Pessary on 05 September 2011. This product is licensed for sale in pharmacies, under the supervision of a pharmacist (legal status P).

Canesten Soft Gel Pessary is a single application for the treatment of thrush. It is inserted into the vagina for treatment at the site of infection.

The active substance in Canesten Soft Gel Pessary is clotrimazole. Clotrimazole belongs to a group of medicines called azoles and is an antifungal agent that 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 Soft Gel Pessary outweigh the risks, hence a Marketing Authorisation has been granted.
CANESTEN SOFT GEL PESSION

PL 00010/0633

SCIENTIFIC DISCUSSION

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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 Soft Gel Pessary (PL 00010/0633) on 05 September 2011. This product is licensed for sale in pharmacies, under the supervision of a pharmacist (legal status P) and is indicated for the treatment of candidal vaginitis.

This is a full-dossier application for a known active substance submitted as a line extension application according to Article 8.3 of Directive 2001/83/EC as amended, cross-referring to Canesten 500mg Pessary (PL 00010/0083) which was first authorised to Bayer plc, UK on 04 January 1982.

Canesten Soft Gel Pessary 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 the product is a line-extension of an approved product licence containing a well-known active substance.

To support this application, data from one new clinical study was submitted, to evaluate the therapeutic equivalence of the soft gel pessary versus the vaginal tablet formulation. The clinical study was conducted in accordance with Good Clinical Practice (GCP). With the exception of this study, no new clinical data were submitted with this application, which is acceptable given that the product is a line-extension of an approved product licence containing a well-known active substance.

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 Soft Gel Pessary 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-chlorotrityl)imidazole
1-[(2-chlorophenyl)-diphenylmethyl]1H-imidazole

Structure:

\[
\text{Clotrimazole is a white to slightly yellowish fine crystalline powder which is practically insoluble in water, freely soluble in ethanol and chloroform, sparingly soluble in ether.}
\]

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

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.

Suitable pharmaceutical development data have been provided for this application.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided.

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

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

**Container Closure System**
Each soft gel pessary is packaged into 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.

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”.
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 product is a line-extension of an approved product licence containing a well-known active substance, no further data have been submitted and none are required. 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 a line-extension of the existing Clotrimazole 500mg Vaginal Tablet, it is not expected to result in a significant increase of use of the clotrimazole based formulations and thus no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

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

PHARMACOKINETICS
No new pharmacokinetic studies have been conducted and this is acceptable. Previous studies using the same dose level have demonstrated that systemic concentrations are negligible.

PHARMACODYNAMICS
No new pharmacodynamic studies have been conducted and this is acceptable.

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:

<table>
<thead>
<tr>
<th>Visit</th>
<th>Vaginal tablets, n (%)</th>
<th>Soft vaginal capsules, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP population:</td>
<td>n = 186</td>
<td>n = 180</td>
</tr>
<tr>
<td>Responder rate, n (%)</td>
<td>123 (66.1%)</td>
<td>132 (73.3%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>59.2%, 73.2%</td>
<td>66.6%, 80.1%</td>
</tr>
<tr>
<td>Difference capsules-tablets (95% CI)</td>
<td>7.2% (-7.3%, 21.7%)</td>
<td></td>
</tr>
<tr>
<td>ITT population:</td>
<td>n = 192</td>
<td>n = 185</td>
</tr>
<tr>
<td>Responder rate, n (%)</td>
<td>126 (65.6%)</td>
<td>134 (72.4%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>58.6%, 72.6%</td>
<td>65.7%, 79.1%</td>
</tr>
<tr>
<td>Difference capsules-tablets (95% CI)</td>
<td>7.2% (-7.3%, 21.7%)</td>
<td></td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Vaginal tablets n = 192 (%)</th>
<th>Soft vaginal capsules n = 185 (%)</th>
<th>Vaginal tablets n = 192 (%)</th>
<th>Soft vaginal capsules n = 185 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with available data (n)</td>
<td>192</td>
<td>185</td>
<td>185</td>
<td>180</td>
</tr>
<tr>
<td>Number of responders, n (%)</td>
<td>162 (84.4%)</td>
<td>163 (88.1%)</td>
<td>172 (93.0%)</td>
<td>167 (92.8%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>79.9%, 89.8%</td>
<td>83.2%, 93.0%</td>
<td>89.0%, 96.9%</td>
<td>88.7%, 96.8%</td>
</tr>
<tr>
<td>Capsules-tablets (95% CI)</td>
<td>3.7% (-8.2%, 15.7%)</td>
<td>0.2% (-10.6%, 10.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects with available data</td>
<td>192</td>
<td>185</td>
<td>185</td>
<td>180</td>
</tr>
<tr>
<td>Number of responders (n)</td>
<td>186 (96.9%)</td>
<td>182 (98.4%)</td>
<td>183 (98.9%)</td>
<td>171 (95.0%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>94.2%, 99.6%</td>
<td>96.3%, 100.5%</td>
<td>97.2%, 100.7%</td>
<td>91.5%, 98.5%</td>
</tr>
<tr>
<td>Capsules-tablets (95% CI)</td>
<td>1.5% (-6.6%, 9.6%)</td>
<td>-3.9% (-12.3%, 4.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycological cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with available data (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of responders, n (%)</td>
<td>149 (77.6%)</td>
<td>149 (81.0%)</td>
<td>150 (81.1%)</td>
<td>138 (77.5%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>71.4%, 83.8%</td>
<td>75.0%, 86.9%</td>
<td>75.2%, 87.0%</td>
<td>71.1%, 83.9%</td>
</tr>
<tr>
<td>Capsules-tablets (95% CI)</td>
<td>3.4% (-9.9%, 16.6%)</td>
<td>-3.6% (-17.0%, 9.9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 Soft Gel Pessary 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 this product in comparison to Clotrimazole 500mg vaginal tablets (Bayer plc, UK) has been established, with no statistically/clinically significant differences observed between products.

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 Clotrimazole 500mg vaginal tablets (Bayer plc, UK). 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.
1 The MHRA received the marketing authorisation application on 09 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 SOFT GEL PESSARY

PL 00010/0633

STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
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</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Canesten Soft Gel Pessary

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Clotrimazole 500mg.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Vaginal capsule, soft
Yellow teardrop-shaped soft capsule

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Canesten Soft Gel Pessary is indicated for the 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.

Children: Not for use in children under 16.

4.3 Contraindications
Hypersensitivity to clotrimazole or any other ingredient in this medicine.

4.4 Special warnings and precautions for use
Medical advice should be sought if this is the first time the patient has experienced symptoms of candidal vaginitis.

Before using Canesten Soft Gel Pessaries, medical advice must be sought if any of the following are applicable:
- more than two infections of candidal vaginitis in the last 6 months.
- previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease.
- pregnancy or suspected pregnancy.
- aged under 16 or over 60 years.
- known hypersensitivity to imidazoles or other vaginal antifungal products.

Canesten Soft Gel Pessaries should not be used if the patient has any of the following symptoms where upon medical advice should be sought:
- irregular vaginal bleeding.
- abnormal vaginal bleeding or a blood-stained discharge.
- vulval or vaginal ulcers, blisters or sores.
- lower abdominal pain or dysuria.
- any adverse events such as redness, irritation or swelling associated with the treatment.
- fever or chills.
- nausea or vomiting.
• diarrhoea.
• foul smelling vaginal discharge.

Patients should be advised to consult their physician if the symptoms have not been relieved within one week of using Canesten Soft Gel Pessary. Canesten 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 overdosage, 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)

Reproductive system and breast disorders:
genital peeling, pruritus, rash, oedema, discomfort, burning, irritation, pelvic pain

Gastrointestinal disorders:
abdominal pain

4.9 Overdose
In the event of accidental oral ingestion, gastric lavage is rarely required and should be considered 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 antisepsics – imidazole derivatives

Clotrimazole is an imidazole derivative with a broad spectrum of antymycotic 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 – 8.0 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.

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.

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

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.

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). The blister and an applicator are enclosed in a cardboard carton.

6.6 Special precautions for disposal
No special requirements.
MARKETING AUTHORISATION HOLDER
Bayer plc
Bayer House
Strawberry Hill
Newbury, Berkshire
RG14 1JA
Trading as Bayer plc, Consumer Care Division

MARKETING AUTHORISATION NUMBER(S)
PL 00010/0633

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

DATE OF REVISION OF THE TEXT
05/09/2011
Module 3
PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully because it contains important information for you. This medicine is available without prescription. However, you still need to use Canesten Soft Gel Pessary carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve in 7 days.
- If you have any unusual effects after using this product, tell your doctor or pharmacist.

IN THIS LEAFLET
1. What is Canesten Soft Gel Pessary and what is it used for?
2. Before you use Canesten Soft Gel Pessary
3. How to use Canesten Soft Gel Pessary
4. Possible side effects
5. How to store Canesten Soft Gel Pessary
6. Further information

1. WHAT IS CANESTEN® SOFT GEL PESSARY AND WHAT IS IT USED FOR?
Canesten Soft Gel Pessary is a single application for the treatment of vaginal thrush. It is inserted into the vagina for treatment at the site of infection.

Only use this product if you have been previously diagnosed by your doctor as having vaginal thrush. The active substance in Canesten Soft Gel Pessary 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® SOFT GEL PESSARY
Do not use Canesten® Soft Gel Pessary:
- If you are allergic (hypersensitive) to clotrimazole or any of the other ingredients of Canesten Soft Gel Pessary (see Section 6. Further information).

Before using Canesten® Soft Gel Pessary, you should see your doctor if:
- You are unsure whether you have thrush or this is the first time you have had these symptoms.
- You have had more than two infections of thrush in the last six months.
- You or your partner have ever had a sexually transmitted disease.
- You are aged under 16 or over 60.
- You have ever had an allergic reaction to Canesten or any other vaginal antifungal products.
- You have any of the following symptoms:
  - Irregular vaginal bleeding.
  - Abnormal vaginal bleeding or a blood-stained discharge.
  - Ulcers, blisters or sores of the vagina or vulva.
  - Lower abdominal pain.
  - Pain or difficulty in passing urine.
  - Fever or chills.
  - Feeling sick or vomiting.
  - Diarrhoea.
  - A foul smelling discharge from the vagina.

This is because Canesten Soft Gel Pessary may not be the right treatment for you.

Special precautions:
As with other 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 Soft Gel Pessary. 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® SOFT GEL PESSARY
If Canesten Soft Gel Pessary has been prescribed for you by your doctor, follow any instructions he/she may have given you. If you purchased this product without a prescription, follow these directions closely:
The applicator should be used to insert the pessary 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 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.

Canesten® Soft Gel Pessary is for use in the vagina only.

Do not put the pessary in your mouth or swallow it. If the pessary is 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 Soft Gel Pessary can cause side effects, although not everybody gets them.

As with all medicines, some people may be allergic to the pessary. 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 Canesten pessary you might experience:

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

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

5. HOW TO STORE CANESTEN® SOFT GEL PESSARY

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 use Canesten Soft Gel Pessary after the expiry date which is stated at one end of the carton and on the foil blister strip of the pessary. 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® Soft Gel Pessary contains:

- 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.

What Canesten® Soft Gel Pessary looks like and contents of the pack:

Canesten Soft Gel Pessary contains a single yellow teardrop-shaped soft vaginal capsule held inside a foil blister pack and one applicator for insertion of the pessary into the vagina.

Marketing Authorisation Holder:

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

Manufacturer:

GP Grenzach Produktions GmbH,
79630 Grenzach-Wyhlen, Germany.

Remember: If you have any doubts about using Canesten® Soft Gel Pessary 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.

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Bayer
Module 4
LABELLING

Carton:

Blister

MHRA PAR – Canesten Soft Gel Pessary (PL 00010/0633)