FOOD AND DRUGS AUTHORITY GHANA

Public Assessment Report

CANESTEN SOFT GEL OVULES 500mg.

Clotrimazole

AFH0040/23

Bayer West Central Africa, KA PMB 177, Office 9th Floor, Emporium (Regus), Movenpick Ambassador Hotel, Independence Avenue, Ridge-Airport, Accra, Ghana

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Administrative info

Dosage Form	Soft Gel Pessaries
Strength	500mg
Applicant's Name & Postal Address	Bayer Consumer Care AG Peter Merian-Strasse 84 Basel, Switzerland
Manufacturer's Name & Address	Bulk Manufactured at: Berlimed S.A Francisco Alonso, 7 28806 Alcalá de Henares, Madrid Spain Packaged and Released by: GP Grenzach Produktions GmbH Emil-Barell-Strasse 7 79639 Grenzach-Wyhlen Germany Marketing Authorisation Holder: Bayer Consumer Care AG Peter Merian-Strasse 84 Basel, Switzerland
Local Agent	Bayer West Central Africa, KA PMB 177, Bayer West Central Africa S A Ghana Representative Office, 9th floor Emporium REGUS, Movenpick Ambassador Hotel Independence Avenue Ridge- Airport, Accra, Ghana

1. Part 1

1.1 Introduction

Based on the review of the data on quality, safety and efficacy, the application for Canesten Soft Gel Ovules 500mg Pessaries indicated for the treatment of vaginal yeast infections (vaginal candidiasis) is approved.

1.2 Executive Summary

1.2.1 About the product

A comprehensive description of the indications and posology is given in the SmPC. This registration application concerns an innovator application.

The marketing authorization has been granted pursuant to section 118 of the Public Health Act, Act 857.

2. Part 2: All accepted presentations (including photo)

3. Part 3: Product information for the user (Patient Information Leaflet - PIL) – annex 1

4. Part 4: Information for the health care provider (Summary of Product Characteristics– SmPC) – annex 2

5. Part 5 Scientific Overview and Discussion

5.1 Introduction

Canesten Soft Gel Ovules-presented as a teardrop soft capsule with a yellow opaque gelatin shell containing a homogenous suspension. Each pessary contains Clotrimazole 500mg. The soft gel pessaries are packed in a thermoform blister strip. Each blister is formed from a clear triplex laminate film of PVC/PVdC/PVC (Total PVC 250µm; PVdC 120g/m2) sealed with 20 µm hard tempered aluminium lidding foil.

The excipients are: gelatin, glycerol, purified water, titanium dioxide, and quinoline yellow.

5.2 Active Pharmaceutical Ingredient(s) (API)

The active pharmaceutical ingredient (API) clotrimazole, is well established and described in the European Pharmacopoeia. The API is a dry white to slightly yellowish fine crystalline powder which is practically insoluble in water, freely soluble in organic solvents.

Manufacturing process

The manufacturing process was presented with sufficient details. The active pharmaceutical ingredient has been adequately characterised and acceptable specifications have been adopted for solvents and reagents.

Quality control of drug substance

The pharmaceutical ingredient specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance

Stability data are provided on the active substance for three (3) batches stored at 30°c. The currently acceptable retest period is 60 months when stored at 30°c.

5.3 Finished Pharmaceutical Product

Pharmaceutical development

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant FDA/ICH guidelines. The choice of excipients, packaging and manufacturing is justified. The main development studies concerned the characterisation of the finished product and the development of the manufacturing process was well discussed.

The list of excipients is included in section 6.1 of SmPC.

The choice of excipients, packaging and manufacturing is justified.

The aim of the pharmaceutical development was to provide a safe and effective soft gel pessaries formulation containing Clotrimazole that is convenient for patients and ensures patient compliance.

Manufacturing process
The manufacturing process consists of gelatin mass preparation, fill preparation, encapsulation, drying, inspection and bulk packaging.. The manufacturing process has been validated according to relevant FDA/ICH guidelines. Process validation data on the product have been presented for at least three production scale batches in accordance with the relevant FDA guidelines.

Control of excipients
The excipients comply with the requirements of Official compendia. These specifications are acceptable.

Microbiological attributes
The drug product is routinely tested for microbial enumeration which is acceptable.

Quality control of finished pharmaceutical products.
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes the following parameters; appearance, uniformity of fill mass, average fill mass, uniformity of dosage units, disintegration, identification of active ingredients, identification of shell colouring agents, assay of active ingredients, degradation products, microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Batch analytical data from at least three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of finished pharmaceutical products.
Stability data on the product have been provided on three production scale batches stored at 30°c. The conditions used in the stability studies are according to the FDA/ICH stability guideline. The batches were stored in the proposed unit dose containers. All parameters remain within the specified limits. The proposed shelf-life of 36 months and 30°c storage condition is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies.
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

5.4 Summary of product safety and efficacy

Canesten Soft Gel Ovules 500mg- Pessaries has been shown to conform to the same relevant standards of quality, efficacy, and safety. The clinical safety of Canesten Soft Gel Ovules 500mg-is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC for data on clinical safety.

6. Part 6 Benefit/Risk Assessment

Based on FDA's assessment of data on quality, safety and efficacy the term of assessors considered that the benefit–risk profile of–Canesten Soft Gel Ovules 500mg- Pessaries was acceptable.

7. Part 7: Steps taken for registration.

The application was processed through the reliance route.

8. Annex 1

CANESTEN SOFT GEL OVULES 500 mg

Clotrimazole

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

- **CANESTEN SOFT GEL OVULES** is available without a doctor's prescription, for you to treat a mild illness. Nevertheless, you still need to use **CANESTEN SOFT GEL OVULES** carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Do not share **CANESTEN SOFT GEL OVULES** with any other person
- Ask your healthcare provider or pharmacist if you need more information or advice
- You must see a doctor if your symptoms worsen or do not improve after seven days

What is in this leaflet.

1. What CANESTEN SOFT GEL OVULES is and what it is used for.

Clotrimazole is an anti-fungal agent.

CANESTEN SOFT GEL OVULES are used for the treatment of vaginal yeast infections which cause vaginal itching, burning, and discharge.

2. What you need to know before you use CANESTEN SOFT GEL OVULES.

Do not use CANESTEN SOFT GEL OVULES:

- If You are allergic to clotrimazole or any of the ingredients of **CANESTEN SOFT GEL OVULES** (listed in section 6)

Warnings and precautions

Take special care/ special care should be taken with **CANESTEN SOFT GEL OVULES**:

- **CANESTEN SOFT GEL OVULES** are not for oral use

- Do not use tampons, intravaginal douches, spermicides or other vaginal products while using **CANESTEN SOFT GEL OVULES**
- Avoid vaginal intercourse while using **CANESTEN SOFT GEL OVULES** because the partner could become infected.
- Seek medical advice if any of the following are applicable:
  - More than two infections of candida 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 sensitivity to imidazoles or other vaginal antifungal products
- Do not use Canesten Soft Gel Ovules if you have any of the following symptoms:
  - Irregular vaginal bleeding
  - Abnormal vaginal bleeding or a blood-stained discharge
  - Vaginal ulcers, blisters or sores
  - Lower abdominal pain or difficult urination
  - Redness, irritation or swelling associated with the treatment
  - Fever or chills
  - Nausea or vomiting
  - Diarrhea
  - Foul smelling vaginal discharge
- If there is no improvement in 3 days or if symptoms have not disappeared in 7 days, then consult a medical practitioner as not all vaginal infections are caused by yeasts.

Children and adolescents:

- Do not use **CANESTEN SOFT GEL OVULES** on girls who are under 16 years

Other medicines and CANESTEN SOFT GEL OVULES:

- Always tell your healthcare provider if you are taking any other medicine (this includes complementary or traditional medicines.)
- Canesten Soft Gel Ovules may reduce the effectiveness and safety of latex products such as condoms and diaphragms. The effect is temporary and occurs only during treatment.

Pregnancy and breastfeeding:

- If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before using **CANESTEN SOFT GEL OVULES**.
- **CANESTEN SOFT GEL OVULES** should not be used in the first 3 months of pregnancy except on the advice of a healthcare professional.
- During pregnancy the CANESTEN SOFT GEL OVULES should be inserted without using an applicator

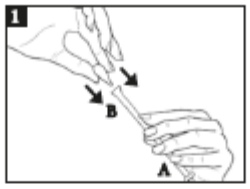
Driving and using machines:

- **CANESTEN SOFT GEL OVULES** has no or negligible influence on the ability to drive or use machinery.

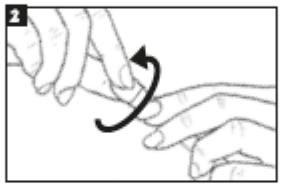
3. How to use CANESTEN SOFT GEL OVULES

- Always use **CANESTEN SOFT GEL OVULES** exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
- One **CANESTEN SOFT GEL OVULE** should be inserted at night into the vagina as high as possible, using the applicator provided. This is best achieved when lying back with legs bent up.

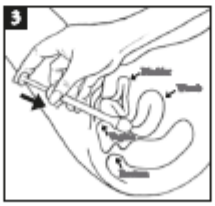
1. Remove the applicator from the packaging. Pull out the plunger A until it stops. Remove the pessary from the foil blister pack and place firmly into the applicator B.



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.

- A single dose treatment will be sufficient for the treatment of fungal infection; however, a second treatment may be carried out if necessary
- It is recommended that the treatment should be timed so as to avoid the menstrual period due to the risk of the ovule being washed out by menstrual flow.
- Not for use in children under 16 years.

If you use more CANESTEN SOFT GEL OVULES than you should:

- In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control center.

4. Possible side effects

CANESTEN SOFT GEL OVULES can have side effects.

Not all side effects reported for CANESTEN SOFT GEL OVULES are included in this leaflet.

Should your general health worsen or if you experience any untoward effects while using **CANESTEN SOFT GEL OVULES,** please consult your health care provider for advice.

The following side effects have been reported and the frequency is unknown, you may need urgent medical attention. Tell your doctor if you notice any of the following:

- Allergic reactions (Fainting, Low blood pressure, Difficult breathing, Hives, Itching, Impaired consciousness).
- Abdominal pain/cramps
- Nausea
- Diarrhea
- Rash
- Increase in urinary frequency
- Swelling in the genitals
- Irritation
- Burning
- Genital peeling
- Pain in the pelvic area

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist. By reporting side effects, you can help provide more information on the safety of **CANESTEN SOFT GEL OVULES**.

5. How to store CANESTEN SOFT GEL OVULES.

- Store all medicines out of reach of children.
- Store at or below 30 °C
- Store in the original carton in a dry place in order to protect from moisture
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets)

6. Contents of the pack and other information

What CANESTEN SOFT GEL OVULES contains:

- The active substance is Clotrimazole 500 mg
- The other ingredients are gelatine, glycerol, lecithin, Liquid paraffin, medium chain triglycerides, sunset yellow, titanium dioxide, quinolone yellow and white soft paraffin.

What CANESTEN SOFT GEL OVULES look like and contents of the pack.

- Soft Gel Ovules are teardrop soft gelatin capsule with a yellow opaque shell
- Each soft gel Ovule is packed into a blister consisting of formed clear PVC/PVdC/PVC laminate film with aluminum lidding foil.

The blister packaged in a folding carton with a leaflet and a disposable applicator.

Bulk Manufactured by:
Berlimed S.A
Francisco Alonso, 7
28806 Alcalá de Henares, Madrid
SPAIN

Packaged and released by:
GP Grenzach Produktions GmbH
Emil-Barell-Strasse 7
79639 Grenzach-Wyhlen
Germany

Annex 2

1. NAME OF THE MEDICINE
Canesten Soft Gel Ovules, 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each soft gel ovule contains clotrimazole 500 mg
For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Canesten Soft Gel Ovules 500 mg is presented as a teardrop softcapsules with a yellow opaque gelatin shell.
Each ovule is contained within a colourless thermoform PVC/PVdC/PVC laminate blister with an aluminium foil lid. The blister is packaged in a folding carton with a leaflet and a disposable applicator.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Canesten Soft gel ovules are indicated for the treatment of vaginal yeast infections (vaginal candidiasis)

4.2 Posology and method of administration
Adults: One Canesten soft gel ovule should be inserted at night into the vagina as high as possible, using the applicator provided. This is best achieved when lying back with legs bent up.
A single dose treatment will be sufficient for the treatment of Candida vaginitis, however a second treatment may be carried out if necessary.

It is recommended that the treatment should be timed so as to avoid the menstrual period due to the risk of the soft gel ovule being washed out by the menstrual flow.

Paediatric population
Not for use in children under 16 years of age

4.3 Contraindications
Hypersensitivity to clotrimazole or any of the ingredients in Canesten Soft Gel Ovules

4.4 Special warnings and precautions for use
Do not use tampons, intravaginal douches, spermicides or other vaginal products while using this product.
Vaginal intercourse should be avoided in case of vaginal infection and while using this product because the partner could become infected

Before using Canesten Soft gel ovules, medical advice should be sought if any of the following are applicable:

- More than two infections of candida 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 sensitivity to imidazoles or other vaginal antifungal products.

Canesten soft gel ovules should not be used if the patient has any of the following symptoms:

- 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 consult their doctor if the symptoms have not been relieved within one week of using Canesten soft gel ovules.
Canesten Soft Gel ovules can be used again if the candida infection returns after seven days. However, if the infection reoccurs more than twice within six months, patients should consult their doctor or healthcare provider.

4.5 Interaction with other medicines and other forms of interaction

Laboratory tests have suggested that, when used together, Canesten Soft Gel Ovules 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 Canesten Soft Gel ovules.

Concomitant use of Canesten Soft Gel Ovules and oral tacrolimus (FK-506, immunosuppressant) might lead to increased tacrolimus plasma levels. Patients should be thus be closely monitored for signs and symptoms of tacrolimus and sirolimus overdosage, if necessary by determination of the respective plasma levels.

4.6 Fertility, pregnancy and lactation

Fertility:
No human studies of the effects of clotrimazole on fertility have been performed, however animal studies have not demonstrated any effects of the drug on fertility

Pregnancy:
There are limited amount of data from the use of clotrimazole in pregnant women. Animal studies with clotrimazole have shown reproductive toxicity at high oral doses (see section 5.3). At the low

systemic exposures of clotrimazole following vaginal treatment, harmful effects with respect to reproductive toxicity are not predicted.

Clotrimazole can be used during pregnancy, but only under the supervision of a doctor or a Healthcare professional.

During pregnancy, Canesten Soft Gel ovules should be inserted without using an applicator.

Lactation:
Available pharmacodynamic/toxicological data in animals have shown excretion of clotrimazole/metabolites in milk after intravenous administration (see section 5.3). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from clotrimazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the Woman

4.7 Effects on ability to drive and use machines
Canesten Soft Gel ovules has no or negligible influence on the ability to drive or use machinery

4.8 Undesirable effects
The following side effects have been reported and the frequency is unknown

Immune system disorders	Allergic reaction (Syncope, hypotension, dyspnoea, urticaria, pruritus)
Gastrointestinal disorders	Abdominal pain
Reproductive system and breast disorder	Genital peeling, pruritus, rash, oedema, discomfort, burning, irritation, pelvic pain, vaginal haemorrhage
General disorders and administrative site conditions	Irritation, burning, contact dermatitis

4.9 Overdose
No risk of acute intoxication is seen as it is unlikely to occur following a single vaginal or dermal application of an overdose (application over a large area under conditions favourable to absorption) or inadvertent oral ingestion. There is no specific antidote. However, in the event of accidental oral ingestion, only supportive care is recommended if clinical symptoms of overdose become apparent (e.g. dizziness, nausea or vomiting).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

A.20.2.2 fungicides
Pharmacotherapeutic group: Gynaecological anti-infectives and antiseptics-
imidazole derivatives

ATC code: G01A F02

Mechanism of action:

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

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 500 mg 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

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity and carcinogenicity.
Clotrimazole was not teratogenic in reproductive toxicity studies in mice, rats and rabbits. In rats high oral doses were associated with maternal toxicity, embryotoxicity, reduced fetal weights and decreased pup survival.

In rats clotrimazole and/or its metabolites were secreted into milk at levels higher than in plasma by a factor of 10 to 20 at 4 hrs after administration, followed by a decline to a factor of 0,4 by 24 hrs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store in the original carton in a dry place in order to protect it from moisture.
Store at or below 30 °C

6.5 Nature and contents of the container

Each soft gel Ovule 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 and other handling

No special requirements

7. MANUFACTURERS.

Bulk Manufactured by:
Berlimed S.A
Francisco Alonso, 7
28806 Alcalá de Henares, Madrid
SPAIN

Packaged and released by:
GP Grenzach Produktions GmbH
Emil-Barell-Strasse 7
79639 Grenzach-Wyhlen
Germany