1.3.1
Summary Of Product Characteristics (SPC)

1.3.1 Summary of Product Characteristics (SPC)

1.3.1.1 Invented Name of the Medicinal Product

CLOVIGAL

Clotrimazole Vaginal Tablets BP

1.3.1.2 Strength

Clotrimazole BP 100 mg

1.3.1.3 Dosage Form

Solid Oral Dosage Form

1.3.1.4. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Uncoated Vaginal Tablet Contains:

Clotrimazole BP .....100 mg

Excipients.....q.s.

For a full list of excipients see section 1.3.1.8.1

1.3.1.5 PHARMACEUTICAL FORM

Uncoated Vaginal Tablets

Almost white elongated U shaped biconvex uncoated tablets, embossed "CLOVIGAL" on one side and other side plain.

1.3.1.6 CLINICAL PARTICULARS

1.3.1.6.1 Therapeutic indications

Treatment of infections of vagina and external female genital organs caused by clotrimazole-sensitive microorganisms such as fungi (usually Candida).

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Adults and adolescents aged 16 years and older

One vaginal tablet deep into the vagina as a single dose in the evening.

If there is no improvement after 7 days, a patient should consult a doctor.

Adolescents aged 12-15 years

In adolescents under 16 years of age, Clotrimazole vaginal tablet should only be used after consulting a doctor. If prescribed in this population (post-menarcheal), the recommended posology is the same as for adults.

Paediatric population

The safety and efficacy in children below 12 years of age have not been established.

Method of administration

One vaginal tablet deep in vagina as a single dose in the evening. The vaginal tablet should be inserted as deeply into the vagina as possible with the applicator included in the package.

During pregnancy the vaginal tablet should be inserted into the vagina with a finger, without the applicator, to prevent injuries to the uterine cervix.

There must be moisture in the vagina for the vaginal tablet to melt completely. Otherwise undissolved pieces of the vaginal tablet may slip out of the vagina. In order to avoid the vaginal tablet is inserted as deeply as possible into the vagina just before going to bed. Treatment with Clotrimazole vaginal tablet should not be performed during the menstrual period. Treatment should be finished before the start of menstruation.

The sexual partner should also undergo local treatment if symptoms, e.g. pruritus, inflammation are present.

1.3.1.6.3 CONTRAINDICATIONS

Hypersensitivity to clotrimazole or to any of the excipients.

1.3.1.6.4 WARNING AND PRECAUTION

Patient should consult a doctor in case of:

- the first vaginal infection
- recurrent infections, at least four infections during the previous year
- fever (≥ 38 °C)
- pain in lower abdomen, back pain
- foul-smelling vaginal discharge
- nausea
- vaginal haemorrhage and/or simultaneous pain in the shoulders

Tampons, vaginal rinses, spermicides or other products for vaginal use should not be used concomitantly with this product.

Intercourse should be avoided during the use of Clotrimazole vaginal tablet because the infection may be transferred to the sexual partner.

The contraceptive efficacy and reliability of latex contraceptives, such as condoms and diaphragms, may be reduced.

Vaginal tablets must not be swallowed.

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Simultaneous use of vaginally administered clotrimazole and orally administered tacrolimus (FK-506, immunosuppressive drug) may lead to increased levels of tacrolimus in plasma and similarly with sirolimus. Therefore, patients using tacrolimus or sirolimus have to be carefully monitored to observe symptoms of overdosage, if necessary by determination of the respective plasma levels.

Clotrimazole is a moderate inhibitor of hepatic microsomal CYP3A4 isoenzyme and a weak inhibitor of CYP2C9 isoenzyme. 3–10% of a local vaginal dose of clotrimazole is absorbed in systemic circulation, which may have an effect on the levels of drugs metabolized via

CYP3A4 isoenzyme in particular, potentially increasing the plasma levels of these agents when used concomitantly. Since the effect on CYP2C9 isoenzyme is weak, and only a small portion of locally administered clotrimazole is systemically absorbed, the effect of clotrimazole on the levels of drugs metabolized via CYP2C9 is 3 low. Therefore, due to the very low absorption of clotrimazole after vaginal application especially of a single 500 mg dose, clotrimazole applied intra-vaginally is unlikely to lead to any clinically meaningful drug interactions.

1.3.1.6.6 PREGNANCY AND LACTATION

Pregnancy

There are limited amount of data from the use of clotrimazole in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of clotrimazole during the first trimester of pregnancy. During pregnancy an applicator should not be used. If the treatment is considered necessary during pregnancy, the treatment should be carried out with clotrimazole vaginal tablets, since these can be inserted without using an applicator. The birth canal should be kept clean particularly during the last 4–6 weeks of pregnancy.

Breast-feeding

During local treatment only minor amounts of clotrimazole are absorbed in blood circulation, but as the clinical studies have not defined excretion in the breast milk it is recommended that as a precautionary measurement lactation is stopped during the treatment.

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.

1.3.1.6.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Clotrimazole vaginal tablet has no influence on the ability to drive vehicles or use machinery.

1.3.1.6.8 UNDESIRABLE EFFECTS

System Organ Class	Common (>1/100 to <1/10)	Uncommon (>1/1000 to <1/100)	Rare (>1/10000 to <1/1000)
Gastrointestinal disorders		abdominal pain	
Immune system disorders			allergic reactions
Reproductive system and breast disorders	burning	pruritus (itching) erythema/irritation	oedema skin rash vaginal haemorrhage

The following adverse reactions have been identified during post-approval use of clotrimazole: because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency i.e. frequency: not known

Reproductive system and breast disorders: genital peeling, discomfort, pelvic pain

1.3.1.6.9 OVERDOSE

No risk of acute intoxication is seen as it is unlikely to occur following a single vaginal application of an overdose or inadvertent oral ingestion. There is no specific antidote. The following adverse reactions have been reported during acute overdose of clotrimazole: abdominal pain, upper abdominal pain, diarrhea, indisposition, nausea and vomiting.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic properties:

Pharmacotherapeutic group: gynecological antiinfectives and antiseptics imidazole derivatives

ATC code: G01AF02

Clotrimazole vaginal tablet contains clotrimazole which is a broad-spectrum antimycotic belonging to the group of imidazoles. Clotrimazole vaginal tablet is intended for the local treatment of gynecological fungal infections.

Mechanism of action

Clotrimazole inhibits the ergosterol synthesis of fungi, leading to structural and functional impairment of the cell membrane (permeability is increased). The broad antimycotic spectrum of clotrimazole in vitro and in vivo includes dermatophytes, yeast fungi (e.g. Candida), mould fungi and other fungi. Under appropriate testing conditions, the MIC values of the above mentioned fungi are in the range of less than 0.062–8.0 microg/ml of active substance. Clotrimazole has a fungistatic or fungicidal effect depending on the concentration of clotrimazole at the site of infection. Activity in vitro is limited to the proliferating fungal elements; fungal spores are only slightly sensitive. In addition to its antimycotic action, clotrimazole also acts on, gram-positive microorganisms (streptococci/staphylococci/Gardnerella vaginalis) and gram-negative microorganisms (Bacteroides). In vitro clotrimazole inhibits the multiplication of Corynebacteria and grampositive cocci - with the exception of Enterococci - in concentrations of 0.5-10 µg/ml substrate. Primarily resistant strains of sensitive fungal species are generally very rare. Development of secondary resistance has been found with therapeutic doses only in isolated cases under clinical conditions.

1.3.1.7.2 Pharmacokinetic properties

Absorption:

Pharmacokinetic studies on dermal and vaginal administration have shown that only a very small amount of the clotrimazole dose is absorbed (3–10% of vaginal dose). Due to the rapid hepatic metabolization of absorbed clotrimazole into pharmacologically inactive metabolites the resulting peak plasma concentrations were less than 0,01 µg /ml after 500 mg vaginal dose of clotrimazole. These concentrations are unlikely to lead to measurable systemic effects or side effects.

Biotransformation: In vitro clotrimazole is a moderate inhibitor of hepatic microsomal CYP3A4 isoenzyme and a weak inhibitor of CYP2C9 isoenzyme. 3–10% of a local vaginal dose of clotrimazole is absorbed in systemic circulation, which may have an effect on the levels of drugs metabolized via CYP3A4 isoenzyme in particular, potentially increasing the plasma levels of these agents when used concomitantly. Since only a small portion of

locally administered clotrimazole is systemically absorbed, the effect of a single 500 mg dose of clotrimazole on the levels of drugs metabolized via CYP3A4 or CYP2C9 is low and unlikely to result in clinically meaningful drug interactions.

1.3.1.7.3 Preclinical safety data

Toxicological studies on vaginal or local application in various animal species have shown that the vaginal and local tolerability of clotrimazole is good. Preclinical data reveal no specific hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development. Clotrimazole has caused fetotoxicity in rats with systemic doses of 100 mg/kg. A study with 3 lactating rats administered 30 mg/kg clotrimazole intravenously showed that the drug was 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.

1.3.1.8 PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of Excipients

Microcrystalline cellulose (Grade 102)
Cross carmellose sodium
Magnesium stearate
Colloidal silicon dioxide

1.3.1.8.2 Incompatibilities

Not applicable.

1.3.1.8.3 Shelf life

Three years.

1.3.1.8.4 Special precautions for storage

Store below 30°C. Protected from light.

1.3.1.8.5 Nature and contents of container

Available as a Alu-Alu blister pack of 6 Tablets. Such one blister is packed in a carton along with pack insert.

1.3.1.8.6 Special precautions for disposal and other Special handling

Not Applicable

1.3.1.9 Marketed by:

AQUATIX PHARMACEUTICALS LIMITED

Real Plaza, Plot 1, Junaid Dosunmu Street,

Central Business District Alausa,

P.O. Box 3560 Ikeja, Lagos State, Nigeria.