

## 1. PRODUCT NAME

Clomazol 1% vaginal cream

Clomazol 2% vaginal cream

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clomazol 1% vaginal cream contains 10 mg/g (1% w/w) of clotrimazole in a cream base.

Clomazol 2% vaginal cream contains 20 mg/g (2% w/w) of clotrimazole in a cream base.

See section 6.1 for the full list of excipients.

## 3. PHARMACEUTICAL FORM

Clomazol 1% vaginal cream is presented as a white smooth semi-solid cream.

Clomazol 2% vaginal cream is presented as a white smooth semi-solid cream.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Clomazol 1% (6-day) and Clomazol 2% (3-day) treatment vaginal creams are indicated for the topical treatment of vulvovaginal candidiasis. Application of the cream to the glans penis of the partner may help prevent re-infection of the female.

### 4.2 Dose and method of administration

#### Clomazol 1% vaginal cream (6-day treatment)

Once daily, preferably in the evening for six successive days, one applicator should be filled with cream (approx. 5 g) and inserted as deeply as possible into the vagina with the patient lying on her back. The 35 g tube of cream for vaginal use provides for six such doses.

#### Clomazol 2% vaginal cream (3-day treatment)

Once daily, preferably in the evening for three successive days, one applicator should be filled with cream (approx. 5 g) and inserted as deeply as possible into the vagina with the patient lying on her back. The 20 g tube of cream for vaginal use provides for three such doses.

#### Generally:

If symptoms persist for more than 7 days or do not improve within 4 days, the patient may have a medical condition that requires treatment by a doctor.

The treatment can be repeated if necessary, however recurrent infections may indicate an underlying medical cause, including diabetes or HIV infection. Patients should seek medical advice if symptoms return within 2 months or they have had 3 or more infections within 6 months.

If the labia and adjacent areas are simultaneously infected, local treatment with an external cream should also be given in addition to the intravaginal treatment (combination treatment). The sexual partner should also undergo local treatment if symptoms e.g. pruritis, inflammation, etc. are present.

Treatment during the menstrual period should not be performed. 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.

Avoidance of vaginal intercourse is recommended in case of vaginal infection and while using this product as the partner could become infected.

Clotrimazole vaginal products are intended for use by adults aged 18 – 60 years, unless use is advised by a doctor.

#### **Paediatric Population**

Clotrimazole vaginal products are intended for use by adults aged 18 – 60 years. There are no data available for paediatric use.

#### **4.3 Contraindications**

Hypersensitivity to the active substance, clotrimazole, or to any of the excipients listed in section 6.1.

#### **4.4 Special warnings and precautions for use**

If the patient has a fever (temperature of 38°C or above), lower abdominal pain, back pain, foul smelling vaginal discharge, nausea, vaginal haemorrhage and/or associated shoulder pain the patient should consult a doctor.

Keep the medicine out of reach of children. Avoid contact with eyes. Do not swallow.

Clotrimazole cream may reduce the effectiveness and safety of latex products such as condoms and diaphragms when applied to the genital area (women: intravaginally, labia and adjacent area of the vulva; men: prepuce and glans of the penis).

*Clomazol creams contain cetostearyl alcohol:* Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

#### **4.5 Interaction with other medicines and other forms of interaction**

Concomitant medication with vaginal clotrimazole and oral tacrolimus (FK-506; immunosuppressant) might lead to increased tacrolimus plasma levels, and similarly with sirolimus. Patients should thus be thoroughly monitored for symptoms of tacrolimus or sirolimus overdose, 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 medicine on fertility.

**Pregnancy (Category A)**

There is a limited amount of clinical data in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Clotrimazole can be used during pregnancy, but only under the direction of a health care professional.

**Lactation**

There is no data on the excretion of clotrimazole into human milk. However, systemic absorption is minimal after administration and is unlikely to lead to systemic effects. Clotrimazole may be used during lactation.

**4.7 Effects on ability to drive and use machines**

The medication has no or negligible influence on the ability to drive or use machinery.

**4.8 Undesirable effects**

Frequencies not known. 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, frequency cannot be estimated from the available data.

**Immune system disorders**

Anaphylactic reaction, angioedema, hypersensitivity.

**Vascular disorder**

Syncope, hypotension

**Respiratory, thoracic and mediastinal disorders**

Dyspnea

**Reproductive system and breast disorders**

Vaginal exfoliation, vaginal discharge, vulvovaginal pruritis, vulvovaginal erythema, vulvovaginal discomfort, vulvovaginal burning sensation, vulvovaginal pain, vaginal haemorrhage.

**Gastrointestinal disorders**

Abdominal pain, nausea.

**Skin and subcutaneous tissue disorders**

Rash, urticaria

**General disorders and administration site conditions**

Application site irritation, oedema, pain

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

#### 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

ATC Code: G01AF02, antifungals for vaginal use – imidazole and triazole derivatives.

##### Mechanism of action

Azoles (e.g. clotrimazole) are usually recommended for the local treatment of vulvovaginal candidosis that is characterised by vulvovaginal symptoms such as itching, burning, discharge, redness, swelling and soreness.

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 primarily 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 gram-positive micro-organisms (Streptococci / Staphylococci / Gardnerella vaginalis) and gram-negative micro-organisms (Bacteroides).

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.

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, suggesting that clotrimazole applied intravaginally is unlikely to lead to measurable systemic effects or side effects.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

The local and systemic tolerance of clotrimazole in different dosage forms was assessed in intravaginal studies in dogs and monkeys and in subacute dermal studies in rabbits. There was no evidence of treatment-related local or systemic adverse effects in any of these studies.

The oral toxicity of clotrimazole has been well-studied.

Following a single oral administration, clotrimazole was slight-to-moderately toxic in experimental animals, with LD50 values of 761 to 923 mg/kg bw for mice, 95 to 114 mg/kg bw for new born rats and 114 to 718 mg/kg bw for adult rats, > 1000 mg/kg bw for rabbits and > 2000 mg/kg bw for dogs and cats.

In repeated dose oral studies conducted in rats and dogs, the liver was found to be the primary target organ for toxicity. This was evidenced by an increase in serum transaminase activities and the appearance of liver vacuolation and fatty deposits starting at 50 mg/kg in the chronic (78-week) rat study and at 100 mg/kg in the subchronic (13-week) dog study.

Clotrimazole has been extensively studied in *in vitro* and *in vivo* mutagenicity assays, and no evidence of mutagenic potential was found. A 78-week oral dosing study of clotrimazole in rats did not show any carcinogenic effect.

In a rat fertility study, groups of FB30 rats received oral doses of clotrimazole up to 50 mg/kg bw for 10 weeks prior to mating and either throughout a 3-week mating period (for males only) or, for females, until day 13 of gestation or 4-week postpartum. Neonatal survival was reduced in the 50 mg/kg bw group. Clotrimazole at doses up to 25 mg/kg bw did not impair the development of the pups. Clotrimazole at all doses did not affect fertility.

No teratogenicity effects were demonstrated in studies in mice, rabbits and rats, given oral doses of up to 200, 180 and 100 mg/kg respectively.

A study with 3 lactating rats administered 30 mg/kg clotrimazole intravenously showed that the medicine was secreted into milk at levels higher than in plasma by a factor of 10 to 20 at 4 hours after administration, followed by a decline to a factor of 0.4 by 24 hours.

Given the limited absorption of clotrimazole after vaginal application (estimated to be 3% - 10%) no hazard is expected from the use of vaginal clotrimazole.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Clomazol 1% and 2% Vaginal Cream:

- Benzyl alcohol
- Cetomacrogol 1000
- Cetostearyl alcohol

- Dimeticone
- Disodium edetate
- Glyceryl monostearate
- Liquid paraffin
- Propylene glycol
- Purified water
- White soft paraffin

## 6.2 Incompatibilities

None known.

## 6.3 Shelf life

3 years.

## 6.4 Special precautions for storage

Store at or below 25°C.

## 6.5 Nature and contents of container

Clomazol 1%: tube containing 35 g of vaginal cream, 10 mg clotrimazole per gram (1% w/w) packed in a carton with six single-use disposable applicators and patient instruction sheet.

Clomazol 2%: tube containing 20 g of vaginal cream, 20 mg clotrimazole per gram (2% w/w) packed in a carton with three single-use disposable applicators and patient instruction sheet.

Not all strengths may be marketed.

## 6.6 Special precautions for disposal

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

## 7. MEDICINE SCHEDULE

Pharmacist only medicine

## 8. SPONSOR

Multichem NZ Ltd

Private Bag 93527

Takapuna

AUCKLAND 0740

Telephone: (09) 478 3841

**9. DATE OF FIRST APPROVAL**

Clomazol 1% vaginal cream- 2/10/2003

Clomazol 2% vaginal cream- 19/06/2008

**10. DATE OF REVISION OF THE TEXT**

07/07/2022

**SUMMARY TABLE OF CHANGES**

SECTION	SUMMARY OF CHANGES
4.6	Updated information for use in Pregnancy and Lactation.
4.8	Updated adverse reactions in sections: <ul style="list-style-type: none"> <li>• Immune system disorders</li> <li>• Reproductive system and breast disorders</li> <li>• Gastrointestinal disorders</li> </ul> New sections added: <ul style="list-style-type: none"> <li>• Vascular disorder</li> <li>• Respiratory, thoracic and mediastinal disorders</li> <li>• Skin and subcutaneous tissue disorders</li> <li>• General disorders and administration site conditions</li> </ul>
5.1	Changed ATC Code to G01AF02 Antifungals for vaginal use – imidazole and triazole derivatives. Additional information added under Mechanism of action.