SUMMARY OF PRODUCT CHARACTERISTICS

1. Name and presentation form of the medicinal product

Clotri-Denk 100 Vaginal

2. Qualitative and quantitative composition

Active ingredient: Clotrimazole.
One vaginal tablet contains 100 mg clotrimazole.
Excipients: Please refer to item 6.1 for a complete list of other excipients.

3. Pharmaceutical form

Vaginal tablet.
For insertion into the vagina
White, bean-shaped vaginal tablet.

4. Clinical particulars

4.1 Therapeutic indications

Vaginal discharge caused by yeasts, vaginal infections where fungi are present or suspected (usually candida species).

4.2 Posology, method and duration of administration

One vaginal tablet is inserted daily as deep as possible for six consecutive days, preferably at night.
Clotri-Denk 100 Vaginal is best given with the patient lying on her back with her legs slightly bent up.
During pregnancy vaginal treatment should be performed without an applicator.
It is not advisable to administer treatment during a period (menstruation). Treatment should be finished before the onset of menstruation. The medication should only be administered during menstruation if symptoms are severe.

To avoid possible re-infection the partner should be examined at the same time.

Generally, a course of treatment lasting 6 days is adequate. The treatment can be repeated where necessary.
The treatment must be applied regularly and for an adequate period of time in order for it to be effective.

4.3 Contra-indications

Clotri-Denk 100 Vaginal should not be used in case of known hypersensitivity to clotrimazole or one of the other ingredients.

Application under medical supervision if: first occurence of the disease, occurence more than 4 times during the last 12 months, the patient is younger than 18 years.

4.4 Special warnings and precautions for use

The concomitant application of latex products (e.g. condom or diaphragma) can cause a reduced function of these products and therefore a reduction in security due to the excipients of *Clotri-Denk 100 Vaginal*.
If treatment during pregnancy is necessary, it should be given without an applicator and/or administered by a doctor.

4.5 Interaction with other medicaments and other forms of interaction

Clotri-Denk 100 Vaginal reduces the efficacy of amphotericin and other polyene antibiotics (nystatin, natamycin).

4.6 Pregnancy and lactation

The findings of an epidemiological study in pregnant women revealed the well-founded suspicion that vaginal use of clotrimazole (imidazole) during the first trimester of pregnancy may cause an increase in the miscarriage rate.
There are no equivalent studies for the 2nd and 3rd trimesters.
Clotrimazole should therefore be administered with the necessary caution, as there are no epidemiological data available that rule out the risk of malformation in humans when administered topically (dermal/vaginal).

If treatment during pregnancy is necessary, it should be given without an applicator and/or administered by a doctor.

It is not known whether clotrimazole is excreted in human milk. Due to the low absorption rate during topical use, use during nursing is not likely to pose any risk for the infant.

4.7 Effects on ability to drive and use machines

There are no studies available on the effect of this drug on the ability to drive.

4.8 Adverse drug reactions

The adverse drug reactions will be described in this section under the headings of the frequency of occurrence, as defined below:

Very common (≥1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1000)
Very rare (< 1/10,000)
Not known: cannot be assessed on the basis of the available data

Occasionally skin reactions may occur, e.g. reddening, burning or stinging.
In single patients generalized hypersensitivity reactions of different intensity may occure. These may afftect the skin (e.g. itching and reddening), respiration (e.g. dyspnea), circulation (decrease of blood pressure whereby treatment is necessary up to reduced state of consciousness), gastro-intestinal system (nausea and diarrhea).

4.9 Overdosage

The toxic dose of oral (!) clotrimazole is very high. Serum concentrations of clotrimazole measured after vaginal or external use are practically non-existent.
There is no special antidote.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Imidazole derivative/broad spectrum antimycotic drug
ATC Code: G01AF02

The mode of action of clotrimazole is primarily fungistatic while at high concentrations it is fungicidal. Clotrimazole only acts on proliferating fungal elements.
Current scientific information suggests that the antimycotic effect of clotrimazole stems from inhibition of ergosterol biosynthesis. Since ergosterol is an essential component of the cell membrane of fungi, the influence of clotrimazole is such that, after a delay due to consumption of the cytoplasmic ergosterol of the fungal cell, major changes occur in composition and properties of the membrane. The attendant impairment of membrane permeability finally leads to cell lysis.
In addition, fungistatic concentrations of clotrimazole interfere with mitochondrial and peroxisome enzymes. As a consequence, the hydrogen peroxide concentrations rise to toxic levels, and this probably leads to necrocytosis (”hydrogen peroxide auto-digestion“).
In vitro and in vivo clotrimazole has a broad spectrum of activity, which includes dermatophytes, fungi, moulds and dimorphic fungi.
Under suitable test conditions the MIC values for these types of fungi are in a range of less than 0.062 – 4 (– 8) µg/ml substrate.

In addition to its antimycotic activity clotrimazole also inhibits in vitro the reproduction of corynebacteria and gram-positive cocci, except for enterococci, in concentration of 0.5 –10 µg/ml substrate and is active with 100 µg/ml of trichomonazide.
In terms of resistance clotrimazole can be classified positively, primary resistant types of fungal species are very rare, secondary resistance development of sensitive fungi have only been observed in very isolated cases under therapeutic conditions.

5.2 Pharmacokinetic properties

Pharmacokinetic experiments after dermal and vaginal application show that only a small part of less than 2 or rather 3 –10 % of the clotrimazole dose is absorbed. Resultant peak plasma concentrations are less than 10 ng/ml and do not result in detectable systemic effects or side-effects.
Clotrimazole undergoes oxidation and degradation of the imidazole ring (deamination, o-dealkylation) in the liver to yield ineffective hydroxy derivatives and is mainly excreted via the bile with the faeces.

5.3 Preclinical safety data

- Acute toxicity

Acute oral toxicity of clotrimazole (LD_{50}) lies between 500 and 900 mg/kg body weight in rodents. Due to vomiting of the investigational medicinal product at doses in excess of 100 mg/kg body weight, it was not possible to measure lethal doses in rabbits, cats or dogs.

- Subacute/subchronic toxicity

Subacute dermal administration in rabbits and vaginal administration of up to 500 mg active ingredient in dogs over a period of 3 weeks revealed local tolerability of the skin and vagina to be good for the test samples used. The active ingredient was not observed to cause primary irritation to the skin or mucous membranes.
Studies on subacute and/or subchronic toxicity (up to 13 weeks) with oral doses of up to 200 mg/kg body weight in dogs and rats revealed changes in the liver-specific blood parameters (transaminases, alkaline phosphatase). Furthermore, macroscopic liver enlargement and microscopic liver cell hypertrophy were observed. There was no evidence of liver cell necrosis. The changes are typical for oral azole antimycotic agents.

- Chronic toxicity

Chronic administration of high oral doses to rats, dogs and monkeys caused changes in the liver and adrenal glands. Dose-dependent liver hypertrophy (cell hypertrophy and increase in total weight) occurred as a result of microsomal enzyme induction in the hepatocytes. (Symptoms of intrahepatic cholestasis or pathological changes were not observed in dogs or monkeys; only rats, owing to their particular sensitivity to clotrimazole, suffered degenerative hypertrophy in the hepatocytes at doses below 200 mg/kg/day). The functional hypertrophy quickly receded after cessation of therapy.

The thickening of the adrenal cortex was caused by increased fat deposition in the zona reticularis and fasciculata; damage to the parenchyma was not observed. These changes also receded rapidly after cessation of therapy, although they persisted longer than did the liver changes.

- Mutagenicity

Potential mutagenic properties were ruled out by means of a Dominate Lethal Test as well as cytological studies of spermatogonia in hamsters with applied doses of 100 mg/kg body weight.

- Teratogenicity

Teratogenicity studies were performed on mice, rats and rabbits and took the form of oral doses of up to 200 mg/kg body weight; 100 mg/kg was also applied to rat vaginas. Clotrimazole did not exert any influence on fertility; the substance is neither embryotoxic nor teratogenic

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6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, sodium lauryl sulphate, hypromellose, cellulose powder), colloidal anhydrous silica, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a dry place below 25 °C.

6.5 Nature and content of container

Sales and sample packages with 6 vaginal tablets and an applicator, packed with a leaflet in a retail box.

6.6 Special precautions for disposal

No special requirements.

6.7 Marketing authorisation holder

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München, Germany

6.8 Marketing authorisation number(s)

Product licence no. in Germany: 24016.00.01

6.9. Date of authorisation in Germany

15.01.1991

6.10. Date of information

03/2009

6.11. Prescription status

Pharmacy only, without prescription