1. NAME OF THE MEDICINAL PRODUCT

Klion-D 100 vaginal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 mg metronidazole and 100 mg miconazole nitrate in each vaginal tablet.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Almost white, slightly biconvex, special almond shaped vaginal tablets with an imprinting "100" on one side.
Length: approx. 24 mm
Height: approx. 14 mm
Surface of fracture is
white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Local treatment of female urogenital trichomoniasis and/or fungal infections.

4.2 Posology and method of administration

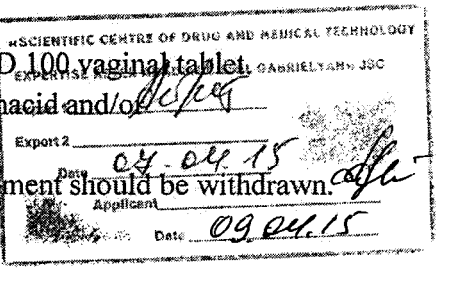
In trichomoniasis: Concurrently with oral metronidazole treatment 1 Klion-D 100 vaginal tablet, slightly moistened before application, should be inserted deeply into the vagina once a day (in the evening, before going to bed) for 10 days.
During the same 10 days 2 (2x250 mg) oral metronidazole tablets should be taken every day (one in the morning and one in the evening) during or after meals without chewing.
Long term recovery can be expected only if the male sexual partner is also treated with oral metronidazole tablets at the same time.
In case of ineffective treatment the 10 day cure can be repeated.
In candidiasis: 1 Klion-D 100 vaginal tablet, slightly moistened before application, should be inserted high up into the vagina once a day (in the evening, before going to bed) for 10 days.

4.3 Contraindications

Hypersensitivity to the active substances or any of the excipients of the preparation. First trimester of pregnancy.

4.4 Special warnings and precautions for use

During Klion-D 100 treatment and at least one day afterwards the consumption of alcoholic beverages is forbidden.
Sexual activity should be avoided during treatment with Klion-D 100 vaginal tablet.
In case of ineffective treatment a changeover to other trichomonacid and/or antifungal systemic treatment is recommended.
If sensitivity, irritation of the mucous membrane develops, treatment should be withdrawn.



4.5 Interaction with other medicinal products and other forms of interaction

No interaction is known with vaginally applied metronidazole and miconazole nitrate until now. If Klion-D 100 vaginal tablet is used together with oral metronidazole tablet, the following drug interactions may develop:

- Metronidazole may potentiate the anticoagulant effect of oral anticoagulants, resulting in a prolongation of prothrombin time, thus their dosage must be re-adjusted.
- Enzyme inductors (e.g. phenytoin, phenobarbital) may accelerate the metabolism of metronidazole, resulting in reduced plasma levels and increased plasma clearance of phenytoin.
- Enzyme inhibitors (e.g. cimetidine) may prolong the half-life and decrease the plasma clearance of metronidazole.
- Consumption of alcoholic beverages during metronidazole therapy may cause disulfiram-like adverse effects (abdominal cramps, nausea, vomiting, headaches and flushing).
- Metronidazole and disulfiram should not be given concurrently (additive effect, psychotic reactions, confusion may occur).
- During metronidazole therapy plasma levels of lithium may increase, therefore the dose of lithium must be decreased or lithium therapy must be discontinued before starting metronidazole therapy.
- In case of concomitant administration of cyclosporine and metronidazole the plasma levels of cyclosporine may increase. If co-administration is necessary, the plasma levels of cyclosporine must be monitored.
- Metronidazole decreases the clearance of 5-fluorouracile and increases its toxicity.
- Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (ASAT, SGOT), alanine aminotranferase (ALAT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose.

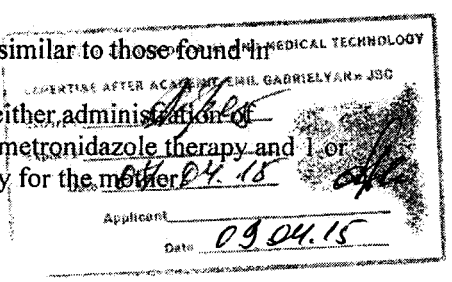
4.6 Pregnancy and lactation

Pregnancy

It is contraindicated in the first trimester of pregnancy.
Oral metronidazole crosses the placental barrier and enters the foetal circulation rapidly.
Reproduction studies have been performed in rats at doses up to five times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to metronidazole.
Metronidazole administered intraperitoneally to pregnant mice at approximately the human dose caused foetotoxocity. However, when administered orally to pregnant mice no foetotoxicity was observed. Nevertheless, there are no adequate and well-controlled studies in pregnant women available.
Based on the meta-analysis of studies performed in the first trimester of pregnancy it has been concluded that no increased foetotoxocity was observed.
In spite of this metronidazole can only be administered during pregnancy and especially in the first trimester of pregnancy after thorough consideration of the expected benefits and possible risks.

Lactation

Oral metronidazole is secreted in breast milk in concentrations similar to those found in plasma. It may cause a bitter taste to breast milk.
To prevent exposure of the infant to the effect of the medicine either administration of metronidazole or breast-feeding should be discontinued during metronidazole therapy and 1 or 2 days afterwards, taking into account the importance of therapy for the mother.



4.7 Effects on ability to drive and use machines

Klion-D 100 vaginal tablets have no influence on the ability to drive and use machines.

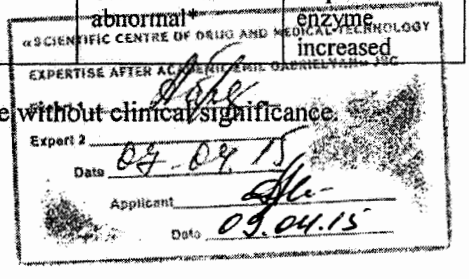
4.8 Undesirable effects

a) During local use of Klion-D 100 vaginal tablets occasionally irritation has been reported. Rarely, local hypersensitivity may occur.

b) Applied together with oral metronidazole tablets the following side effects of metronidazole might occur:

System Organ Class (MedDRA 12.1)	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000
Infections and infestations				Fungal superinfection (e.g. Candidiasis)	
Blood and lymphatic system disorders					Neutropenia (Leukopenia) Thrombocyto-penia
Immune system disorders					Anaphylactic reaction
Metabolism and nutrition disorders			Decreased appetite		
Psychiatric disorders				Confusional state	
Nervous system disorders	Headache		Neuropathy peripheral (Hypoaesthesia) Dizziness Convulsion Coordination abnormal Somnolence Dysgeusia (Metallic taste)		
Gastrointestinal disorders	Nausea	Abdominal pain Abdominal cramps[LLT] Diarrhoea	Vomiting Tongue coated		
Hepatobiliary disorders					Cholestasis Jaundice
Skin and subcutaneous tissue disorders			Angioedema Pruritus Rash Urticaria		Erythema multiforme
General disorders and administration site conditions			Application site irritation Pyrexia		
Investigations				Urine colour abnormal*	Hepatic enzyme increased

* Darkened urine is caused by the metabolite of metronidazole without clinical significance.



c) Peripheral neuropathy (numbness of extremities), headache, convulsions, somnolence, dizziness, abnormal coordination and confusion have been rarely observed during long term, high-dose treatment.

After dose reduction or discontinuation of therapy all symptoms listed in the above table cease spontaneously.

4.9 Overdose

For intravaginal use only. If accidental ingestion of large quantities occurs, gastric lavage can be used. In case of toxic symptoms of overdosage (nausea, vomiting and ataxia) symptomatic therapy such as gastric lavage, activated charcoal, haemodialysis should be applied, as there is no specific antidote. Metronidazole and its metabolites can be dialysed well.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: gynaecological anti-infectives and antiseptics (excluding combinations with corticosteroids), combinations of imidazole derivatives, ATC code: G01A F20

Metronidazole is a local and oral medicine against trichomoniasis.
Miconazole nitrate is an effective antimycotic agent against dermatophytes and Candida species; furthermore, it has a strong bacteriostatic activity on certain Gram-positive bacteria, when applied locally. The purpose of the local application of this combined medicine is the local treatment of trichomoniasis and prevention of vaginal mycosis, which often manifests itself following metronidazole treatment.
It can be used for the treatment of vaginal mycoses occurring on their own.

5.2 Pharmacokinetic properties

There is little absorption through mucous membrane when *metronidazole* and miconazole nitrate are *applied topically*. Neither metronidazole, nor miconazole nitrate is absorbed in detectable amounts. This implies values under 0.2 µg/ml and 0.3 µg/ml, respectively.
Oral metronidazole is usually well absorbed with peak plasma concentration occurring between one and three hours. Single oral administration of 250 mg produced a peak plasma concentration of 5
µg/ml determined with gascromatographic analysis. The bioavailability of the oral preparation is almost 100%.
According to studies performed in healthy volunteers and in patients, metronidazole rapidly penetrates into the cerebrospinal fluid and it reaches therapeutic concentrations in the cerebral abscess and pulmonary abscess. It has high distribution volume and less than 20 % of the circulating metronidazole is bound to plasma proteins. It enters the biliary tract and it reaches concentrations as high as in the plasma. The average elimination half-life of metronidazole is 8 hours in healthy humans. The major route of elimination of metronidazole and its metabolites is via the urine (60-80 % of the dose) with faecal excretion accounting for 6-15 % of the dose.

5.3 Preclinical safety data

The toxicity of metronidazole during long term administration varies between strains of mice and different animal species; the neurological disturbances exhibited by dogs have not been observed with other animal species.
High oral doses caused weight loss and testicular atrophy in one strain of mouse and rat, whilst intravenous metronidazole did not influence the rate of weight gain in rats or produce any significant changes in blood pressure or in haematological or biochemical values. Histological

liver changes without associated changes in serum enzyme levels occurred in monkeys at high doses.
Doses up to 1 mg/kg daily for 5 weeks did not produce a dominant lethal effect in the mouse.
An increased incidence of lung tumours and malignant lymphoma have been reported in Swiss mice studied at one laboratory, but not in Sprague-Dawley rats or hamsters studied by other investigators. Metronidazole has shown mutagenic activity in a number of *in vitro* assay systems, but studies in mammals *in vivo* failed to demonstrate a potential for genetic damage.

The acute and chronic oral toxicity studies in mice, rats, guinea pigs and dogs have provided favourable results which are not negligible even with Klion-D 100 vaginal tablets where miconazole is topically applied.
Teratological studies showed that 80-160 mg of the agent mixed into 100 g food had no teratogenic effect in pregnant animals. The incidence of pregnancy did not differ from that in the untreated control animals, the frequency of implantations and the weight of foetuses were normal, malformations were not observed.
Neither haematological nor biochemical and histopatological alterations could be detected in female monkeys given 5 mg/kg/day doses in the vaginal route.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium laurylsulfate; silica, colloidal anhydrous; magnesium stearate; povidone; sodium hydrogen carbonate; tartaric acid; sodium starch glycollate (Type A); crospovidone; hypromellose, lactose monohydrate (473 mg).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30 °C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

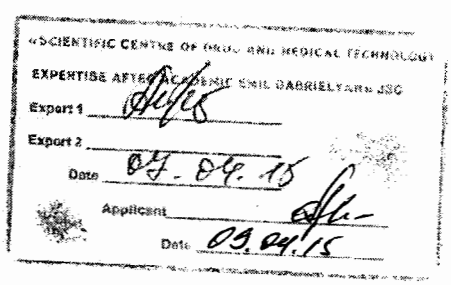
10 vaginal tablets in a strip of soft aluminium foil per carton box.

6.6 Special precautions for disposal and other handling

Note: ✠ (Single cross)
Availability: **group II.**
Medicinal product subject to medical prescription (V).
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gedeon
Richter Plc.
H-1103
Budapest
Gyömrői út
19-21.
Hungary



8. MARKETING AUTHORISATION NUMBER(S)

OGYI-T-3712/01 (Hungary)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 August 1988 / 18 February 2004 / 7 October 2009

10. DATE OF REVISION OF THE TEXT

7 October 2009