STEDMAN

ANNEX IV

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

Drez-V Gel (Miconazole Nitrate and Metronidazole Gel)

1.1 Strength

Miconazole Nitrate	BP	2.0% w/w
Metronidazole	BP	1.0% w/w
Gel Base	q.s	

1.2 Pharmaceutical Dosage Form:

Topical – Vaginal Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

Miconazole Nitrate	BP	2.0% w/w
Metronidazole	BP	1.0% w/w
Gel Base	q.s	

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM:

White, semi solid mass with pleasant odour.

4 CLINICAL PARTICULARS:

4.1 Therapeutic indications

Drez-V Gel is indicated for the topical treatment of mixed vaginal infections of bacterial or candidal origin.

4.2 Posology

FOR INTRAVAGINAL USE ONLY.

One applicator full of Drez-V gel (5g) should be introduced into the vagina daily at bed time for 5 days. The vaginal gel should be applied as deeply as possible into the vagina.

Directions for using the applicator

1. Remove the cap from the tube and attach the applicator in its place and screw it tight.
2. Squeeze the tube from the bottom to fill the gel into the cylinder and push out the plunger up to the marking.
3. Always roll the tube from the bottom to allow easy filling of the applicator and complete utilisation of the contents.
4. Remove the filled applicator from the tube and close the tube with the cap.
5. Hold the filled applicator by the cylinder and gently insert the applicator into the vagina as deeply as possible. Press the plunger completely to empty the contents of the applicator. With the plunger still depressed, remove the applicator from the vagina holding it by the cylinder.

Insertion can be carried out more easily when lying on the back with the knees bent and spread out.

6. Do not reuse the applicators. Discard the applicator after every use.

4.3 Method of administration

Topical

4.4 Contraindications

Drez-V Gel is contraindicated in those patients known to be sensitive to Miconazole Nitrate or Metronidazole or any of the components of the formulation of **Drez-V Gel**. **Drez-V Gel** is also contraindicated in patients with evidence of or a history of blood dyscrasias as well as those with active organic disease of the central nervous system

4.5 Special warnings and precautions for use

Drez-V Gel should be discontinued if sensitisation or irritation is reported during use. Intractable candidiasis may be the presenting symptom of unrecognised diabetes; thus appropriate urine/blood studies may be indicated in patients not responding to treatment with **Drez-V Gel**. During treatment with **Drez-V Gel**, to avoid re-infection, it is recommended that the patient refrains from sexual intercourse or that the male partner wears a condom. It may also be necessary for the male partner to be treated

at the same time as the patient. Alcoholic beverages and drugs containing alcohol should not be consumed by patients being treated with **Drez-V Gel** for at least a day after treatment as nausea, vomiting, abdominal cramps, headaches, tachycardia and flushing may occur. There is the possibility of a disulfiram-like reaction. Use this medication as prescribed by your doctor or on advice of your pharmacist.

4.6 Paediatric population

Not recommended for paediatric use.

4.7 Interaction with other medicinal products and other forms of Interactions

Due to the limited systemic availability after topical application, clinically relevant interactions are rare. However, in patients on oral anticoagulants, such as warfarin, caution should be exercised and anticoagulant effect should be monitored. **Drez-V Gel** can interact with lithium therapy.

4.8 Additional information on special populations

Datas are not available for special population.

4.9 Paediatric population

Not recommended for paediatric use.

4.10 Fertility, Pregnancy and lactation

4.10.1 General principles

Patients who are pregnant or breast feeding should use the product only after consultation with the doctor. Pregnant women should exercise caution in the insertion of the vaginal applicator when using **Drez-V Gel**.

4.10.2 Women of childbearing potential/ Contraception in males and females

No data available.

4.10.3 Pregnancy

Patients who are pregnant or breast feeding should use the product only after consultation with the doctor. Pregnant women should exercise caution in the insertion of the vaginal applicator when using **Drez-V Gel**.

4.10.4 Breastfeeding

Patients who are pregnant or breast feeding should use the product only after consultation with the doctor.

4.10.5 Fertility.

No data available on male and female fertility.

4.11 Effects on ability to drive and use machines

Drez-V Gel is for External Use Only. So this section is not applicable for the product.

4.12 Undesirable effects

Occasionally local side effects such as rash, itching and redness may be associated with the use of **Drez-V Gel**.

In trials with Miconazole Nitrate 100 mg Cream, 1.6% of patients reported effects such as increased discharge, burning, itching or irritation during therapy, that were possibly drug-related. The most frequently reported side effects with vaginal use of Metronidazole were related to the genital tract, including vaginal discharge, symptomatic candidiasis and vulvovaginal irritation. Gastrointestinal side effects, commonly reported following oral Metronidazole therapy, were minimal with intravaginal use.

4.13 Overdose

Overdosage of Miconazole Nitrate in humans has not been reported to date.

Overdosage with Metronidazole appears to be associated with very few abnormal signs or symptoms. Disorientation, ataxia and vomiting may occur, especially after ingestion of large amounts. Early gastric lavage is recommended. In case of suspected massive overdosage, a symptomatic and supportive treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES:

CLINICAL PHARMACOLOGY

Bacterial vaginosis, formerly known as nonspecific or *Gardnerella vaginitis*, is a polymicrobial infection of the vagina. Current data support the concept that bacterial

vaginosis is a polymicrobial syndrome. Organisms that are found with greater frequency and in greater numbers in women with bacterial vaginosis include *Gardnerella. Vaginalis, Mycoplasma hominis, Bacteroides sp., Peptostreptococcus sp., Eubacterium sp., Fusobacterium sp., Prevotella sp*., and other anaerobes.
Candida vaginitis ranks as the second most common cause of vaginal infections. Between 80% and 90% of cases of *Candida vaginitis* arise from infection with *Candida albicans*, with the remaining cases arising from infection with non-*Candida albicans species*, such as *Candida glabrata, Candida tropicalis*, and *Saccharomyces cerevisia*.

DREZ-V Gel contains Miconazole Nitrate and Metronidazole as the active substances. Miconazole Nitrate exhibits in vitro fungi static activity against species of the genus *Candida*.

5.1 Pharmacodynamic properties

Miconazole Nitrate:

Miconazole appears to act on the fungal cell wall and membranes inducing permeability changes which alter the ionic macromolecular composition of the affected cells. Depending on the concentration and duration of exposure in vitro, the yeast cells show progressive cytoplasmic deterioration and prominent shape change, finally resulting in complete cell necrosis. In vivo imidazole antifungal agents exert mainly a fungi static effect. For the treatment of vulvovaginal candidiasis, topical antimycotic imidazole such as Miconazole is preferred since the active concentration of the drug at the site of infection far exceeds the minimum inhibitory concentration. Topical Miconazole formulations are well tolerated and achieve cure rates in excess of 80%.

Metronidazole:

Metronidazole is a member of the imidazole class of anti-bacterial agents and is effective against a wide variety of anaerobic bacteria. The intracellular targets of action of Metronidazole on anaerobes are largely unknown. Its mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of Metronidazole has been reduced by bacterial nitroreductases to an unstable intermediate, which interacts with DNA, effectively preventing further replication.

Metronidazole has been found to be active in vitro against most strains of the following organisms that have been reported to be associated with bacterial vaginosis: *Bacteroides spp., Gardnerella vaginalis, Mobiluncus spp.., Peptostreptococcus spp.*

5.2 Pharmacokinetic properties

Miconazole Nitrate:

Following intravaginal administration of Miconazole Nitrate, small amounts are absorbed. Eight hours after application of 100 mg of Miconazole Nitrate Vaginal Cream, 90% of Miconazole Nitrate is still present in the vagina. Unchanged Miconazole could not be traced in blood plasma or urine. Systemic absorption of Miconazole Nitrate after intravaginal administration is limited.

Metronidazole:

Intravaginally administered Metronidazole is absorbed systemically; but peak serum concentrations after intravaginal administration are < 2% of the levels achieved with 500 mg oral doses.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Metronidazole

Human data

Metronidazole has a very high margin of safety. No lethal dose has been described in humans as yet.

Information about toxic doses of miconazole is not available for humans

Children

Metronidazole has a very high margin of safety. No lethal dose has been described in humans as yet.

Information about toxic doses of miconazole is not available for children.

Relevant animal data

LD_{50} oral (rats)	1 to 5 g/kg
LD_{50} oral (mice)	1 to 5 g/kg

No serious toxicity has been reported in rats dosed with Metronidazole at 150 mg/kg/day, dogs at 50 to 75 mg/kg/day or monkeys at 225 mg/kg/day.

Promotion of pulmonary tumour at a very high level in the mouse (500 mg/kg/day), produced a statistically significant increase in live tumours. Two lifetime studies in hamsters were negative.

In higher doses, testicular dystrophy and prostatic atrophy have been reported in rats and dogs which showed ataxia, muscular atrophy and tremors.

In long-term toxicity studies involving rats for 2 years (normal life span) high doses have been given and the results have been conflicting. Cohen (1973) reported no increase in tumour incidence, while Rustia & Shubik (1972) found increased incidence of tumours in male mice, female mice showed increased incidence of lung tumour, but absolute incidence was actually less than male mice controls. Female mice also had lymphomas more often when given two higher doses.

Miconazole

Human data

Adults: Information about toxic doses not available for humans.

Children:

No data available.

Animal data:

A developmental toxicology study with rats resulted in dose-related reduced body weight gain, rales, and increased salivation. No observable malformations or significant developmental toxicity were found at any dose level tested.

LD_{50} oral (mice) 578.1 mg/kg

LD_{50} oral (rats) >640 mg/kg

LD_{50} oral (guinea pigs) 275.9 mg/kg

LD_{50} oral (dogs) >160 mg/kg

Carcinogenicity

No data is available in humans regarding carcinogenic potential of Metronidazole. Studies in mice and rats reported carcinogenic potential in rodents after high oral dose (Voogel, 1981).

Chronic/carcinogenicity studies in test animals with Miconazole have not been performed (Physician's Desk Reference, 1989).

Teratogenicity

Metronidazole crosses the placental barrier and enters fetal circulation. Studies in rats in doses upto 5 times human doses have not reported any harm to foetuses. Although Metronidazole has been given in all the stages of pregnancy orally no adverse report has been received. However, it is not recommended for use in first trimester of pregnancy.

In nursing mothers and neonates there have not been any well controlled studies, but because Metronidazole appears in breast milk in concentration similar to serum, Metronidazole should not be used except for amoebiasis.

In animals Miconazole has not shown teratogenic effects but is embryotoxic following high oral doses. In the rat studies dystocia was reported at and above 80 mg/kg. These various effects were not seen in rats tested with intravaginal products.

There has been no increase in congenital malformations in pregnant patients using vaginal preparations Reproduction studies showed that in rats and rabbits at intravenous doses of 40 and 20 mg/kg respectively there was no indication of embryotoxicity or teratogenicity.

Mutagenicity

Metronidazole is mutagenic in rodents in high doses for prolonged periods. It is also mutagenic in bacteria (Voogde, 1981). Mutagenic activity associated with Metronidazole has been reported in the urine of patients receiving therapeutic doses. No data available is available about the mutagenic potential of Miconazole.

6 Pharmaceutical Particulars :

6.1 List of excipients

Methyl Hydroxybenzoate, Disodium Edetate, Carbomer 934 P, Triethanolamine, Propylene Glycol, Propyl Hydroxybenzoate, Macrogol 6000, Fragrance & Purified Water.

6.2 Incompatibilities: None reported.

6.3 Shelf life: 24 months

6.4 Special precautions for storage:

Do not below 30°C. Protect from light. Do not freeze. Keep out of reach of children.

6.5 Nature and contents of container:

White Semi solid mass with pleasant odour is packed in an aluminium tube of 30g in an inner carton which is packed along with 5 applicators and pack insert in an outer carton.

6.6 Special precaution for disposal and other handling

No special requirement.

7. Marketing Authorization Holder and Manufacturing Site Address:

Manufactured By

STEDMAN PHARMACEUTICALS PRIVATE LTD.

C-4, SIDCO Pharmaceutical Complex

Alathur, Thiruporur 603 110

Tamil Nadu, INDIA

Tel. 91-44-2744 4502 /4405

E-mail: contactus@stedmanpharma.com

www.stedmanpharma.com

8. Marketing Authorization Number:

9. Date of first registration/renewal of the registration: -

10. Date of revision of the text: May 2018

11. Dosimetry (if applicable)

Not applicable

12. Instructions for preparation of Radio pharmaceuticals (if applicable)

Not applicable