National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

BLEORDERM - V

(Metronidazole and Clotrimazole Cream)

1. NAME OF THE MEDICINAL PRODUCT

Metronidazole and Clotrimazole Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Metronidazole BP	10 % w/w
Clotrimazole BP	2 % w/w

In calcium lactate : lactic acid buffered base

Preservatives

Methylparaben BP	0.2 % w/w
Propylparaben BP	0.1 % w/w
Cream base	q.s.

3. PHARMACEUTICAL FORM

Cream

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

The cream should be administered intravaginally using the applicator supplied.

Adults: The contents of the filled applicator (5g) should be inserted as deeply as possible into the vagina, preferably at night. A second treatment may be carried out if necessary.

Generally: treatment during the menstrual period should not be performed due to the risk of the cream being washed out by the menstrual flow. The treatment should be finished before the onset of menstruation.

Children: Not for use in children under 16.

4.2 Posology and method of administration:

The cream should be administered intravaginally using the applicator supplied.

Adults: The contents of the filled applicator (5g) should be inserted as deeply as possible into the vagina, preferably at night. A second treatment may be carried out if necessary.

Generally: treatment during the menstrual period should not be performed due to the risk of the cream being washed out by the menstrual flow. The treatment should be finished before the onset of menstruation.

Children: Not for use in children under 16.

4.3 Contraindication:

Hypersensitivity to the active substance or to any of the excipients.

Do not use the cream to treat nail or scalp infections.

4.4 Special warnings and precautions for use

Patients should be advised to consult their physician if the symptoms have not been relieved within one week of using BLEORDERM V Cream. It can be used again if the candidal infection returns after 7 days. However, if the candidal infection recurs more than twice within six months, patients should be advised to consult their physician.

Use during menses is not recommended.

Known or previously unrecognised candidiasis may present more prominent symptoms during therapy with BLEORDERM V CREAM and may require treatment with a candicidal agent.

If irritation does occur the patient should be advised to use metronidazole less frequently or to stop temporarily and to seek medical advice if necessary.

Metronidazole is a nitroimidazole and should be used with care in patients with evidence of a history of blood dyscrasias.

As with all vaginal infections, sexual intercourse during the infection and during treatment with BLEORDERM V CREAM is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Laboratory tests have suggested that, when used together, this product may cause damage to latex contraceptives. Consequently the effectiveness of such contraceptives may be reduced. Patients should be advised to use alternative precautions for at least five days after using this product.

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 closely monitored for signs and symptoms of tacrolimus or sirolimus overdosage, if necessary by determination of the respective plasma levels.

Oral metronidazole has been associated with a disulfiram-like reaction in combination with alcohol. Acute psychotic reactions and confusion have occurred during concomitant use of disulfiram with oral metronidazole. At the low serum concentrations which result from the use of BLEORDERM V CREAM, the possibility of similar reactions is unlikely although cannot be excluded.

Oral metronidazole has been shown to increase the plasma concentrations of warfarin and other coumarin anticoagulants resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is unknown. It has also been shown to increase the plasma concentrations of lithium, cyclosporin and 5-fluorouracil. Similar effects after vaginal administration of metronidazole are not expected due to the low plasma concentrations but cannot be completely ruled out.

Metronidazole may interfere with certain types of determination of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactic dehydrogenase (LDH), triglycerides and hexokinase glucose. Values of zero may be observed.

4.6 Fertility, pregnancy and lactation General principles

Pregnancy

There are limited amount of data from the use of clotrimazole in pregnant women. At the low systemic exposures of clotrimazole following vaginal treatment, harmful effects with respect to reproductive toxicity are not predicted.

Clotrimazole can be used during pregnancy, but only under the supervision of a physician or midwife.

During pregnancy the treatment should be carried out with clotrimazole pessary, since these can be inserted without using an applicator.

Data on a large number (several hundred) of exposed pregnancies indicate no adverse effects of metronidazole on the foetus/newborn child. There have been no formal studies with Clotrimazole in pregnant women. Caution should, therefore, be exercised when prescribing to pregnant women.

Breast- feeding

A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from clotrimazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

The ratio of serum concentrations of BLEORDERM V CREAM /oral metronidazole is approximately 0.02. Metronidazole is excreted in milk at concentrations similar to those in maternal serum and the ratio of serum concentrations of metronidazole in the breastfed infant/mother is approximately 0.15. Caution should be exercised when prescribing to lactating women.

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

BLEORDERM V CREAM has no or negligible influence on the ability to drive or use machinery.

4.8 Undesirable effects

Immune system disorders: allergic reaction (syncope, hypotension, dyspnea, urticaria, pruritus). *Reproductive system and breast disorders:* genital peeling, pruritus, rash, oedema, erythema, discomfort, burning, irritation, pelvic pain, vaginal haemorrhage. Gastrointestinal disorders: abdominal pain.

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. However, in the event of accidental oral ingestion, routine measures such as gastric lavage should be performed only if clinical symptoms of overdose become apparent (e.g. dizziness, nausea or vomiting). Gastric lavage should be carried out only if the airway can be protected adequately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Gynaecological antiinfectives and antiseptics – imidazole derivatives

ATC code: G01A F02.

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 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.

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.

Metronidazole is a synthetic antibacterial agent which also possesses amoebicidal activity. BLEORDEM V CREAM has been shown in vivo to be active against the vaginal pathogens Gardnerella vaginalis and bacteroides species.

5.2 Pharmacokinetic properties:

5.3 Pharmacokinetic investigations after vaginal application have shown that only a small amount of clotrimazole (3 – 10% of the dose) 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 500mg dose were less than 10 ng/ml, reflecting that clotrimazole applied intravaginally does not lead to measurable systemic effects or side effects.

Bioavailability studies on the administration of a single 5 gram dose of BLEORDERM V CREAM into the vagina of 12 normal subjects showed a mean Cmax serum concentration of 237 nanogram/ml or about 2% of the mean maximum serum concentration of a 500 mg tablet taken orally (mean Cmax = 12,785 ng/ml). Under normal usage, the formulation therefore affords minimal serum concentrations of metronidazole.

Metronidazole has a large apparent volume of distribution and has the ability to penetrate the blood brain barrier and blood cerebro-spinal fluid barrier at concentrations similar to serum concentrations.

Metronidazole is metabolised in the liver by side chain oxidation and glucuronide formation and a large portion of the absorbed dose is excreted as metabolites. Both unchanged drug and metabolites are excreted mainly in the urine.

5.4 Preclinical safety data:

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity and carcinogenicity.

Clotrimazole was not teratogenic in reproductive toxicity studies in mice, rats and rabbits. In rats high oral doses were associated with maternal toxicity, embryotoxicity, reduced fetal weights and decreased pup survival.

In rats clotrimazole and/or its metabolites were 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.

There is no human experience of overdosage with BLEORDERM V CREAM. There is no specific treatment. Metronidazole is readily removed from the plasma by haemodialysis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Methyl Paraben BP

Propyl Paraben BP

Calcium Lactate BP

Propylene Glycol BP

Polyethene Glycol – 400 BP

Polyethylene Glycol – 4000 (Macrogol) IHS,

6.2 Incompatibilities: NONE

6.3 Shelf life:

36 months from the date of manufacture.

6.4 Special precautions for storage:

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container:

20 gm tube

6.6 Special precautions for disposal and other handling:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

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