Professional Information for BIO-METRONIDAZOLE range

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BIO-METRONIDAZOLE 200 tablets

BIO-METRONIDAZOLE 400 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BIO-METRONIDAZOLE 200 tablet contains 200 mg metronidazole.

Each BIO-METRONIDAZOLE 400 tablet contains 400 mg metronidazole.

BIO-METRONIDAZOLE 200 tablets contain sugar (200 mg lactose per tablet).

BIO-METRONIDAZOLE 400 tablets contain sugar (150 mg lactose per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

BIO-METRONIDAZOLE 200: A white coloured, biconvex uncoated tablet, with ‘MZL / 200’ engraved along with a break line on one side and plain on the other side.

BIO-METRONIDAZOLE 400: A white coloured, biconvex uncoated tablet, with ‘MZL / 400’ engraved along with a break line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

a) In the oral treatment of:

- urogenital trichomoniasis
- non-specific vaginitis
- all forms of amoebiasis
- acute ulcerative gingivitis (Vincent's angina)
- giardiasis
- acute pericoronitis

b) Treatment of infections in which anaerobic bacteria have been identified or are suspected as pathogens, particularly *Bacteroides fragilis* and other species of bacteroides and including other species for which metronidazole is bactericidal, such as fusobacteria, clostridia, eubacteria and anaerobic streptococci.

BIO-METRONIDAZOLE has been used successfully for anaerobic infections in the following conditions: pelvic inflammatory disease and postoperative wound infections.

Combined therapy is often indicated as there are usually mixed infections.

c) Prevention of post-operative infections due to anaerobic bacteria:

i) Given before and after gynaecological surgery

ii) Given before and after appendectomy

iii) Given before and after colonic surgery

d) Treatment of *Helicobacter pylori*-associated gastritis and duodenal ulcer. BIO-METRONIDAZOLE is used in combination with other appropriate therapy.

4.2 Posology and method of administration

Posology

	DURATION OF DOSAGE IN DAYS	**ADULTS**	**CHILDREN 7 TO 10 YEARS**
UROGENITAL TRICHOMONIASIS	1	2 g as a single dose	
Where re-infection is likely,	7	200 mg three times daily or 400 mg twice daily	100 mg three times daily

in adults the consort should receive a similar course of treatment concurrently.	2	800 mg in the morning and 1,2 g in the evening	
NON-SPECIFIC VAGINITIS	7	400 mg twice daily	
	OR 1	2 g as a single dose	
AMOEBIASIS a) Invasive intestinal disease in susceptible subjects.	5	800 mg three times daily	400 mg three times daily
AMOEBIASIS b) Intestinal disease in less susceptible subjects and “chronic amoebic hepatitis”.	5 to 10	400 mg three times daily	200 mg three times daily
AMOEBIASIS c) Amoebic liver abscess, also other forms extra-intestinal amoebiasis	5	400 mg three times daily	200 mg three times daily
AMOEBIASIS d) Symptomless cyst passers	5 to 10	400 to 800 mg three times daily	200 to 400 mg three times daily
GIARDIASIS A second course of treatment may be necessary for some patients two weeks after the end of the first course.	3	2 g once daily	1 g once daily
ACUTE ULCERATIVE GINGIVITIS	3	200 mg three times daily	100 mg three times daily
ACUTE PERICORONITIS	3 to 7	200 mg three times daily	

Anaerobic Infections:

a) Treatment:

BIO-METRONIDAZOLE may be given alone or concurrently with other bacteriologically appropriate antibacterial medicines. They should be given for 7 days or longer depending on clinical and bacteriological assessments of the patient's condition.

Adults: Initially, 800 mg followed by 400 mg by mouth every 8 hours.

Children: 7,5 mg/kg body mass by mouth every 8 hours.

b) Prevention:

Adults: Administered in doses similar to those used for the treatment of established infection. 400 mg may be given every 8 hours in the 24 hours before surgery followed postoperatively by intravenous or rectal administration until oral therapy is possible.

Children: as for treatment (a).

Treatment of *Helicobacter pylori*-associated gastritis and duodenal ulcer:

BIO-METRONIDAZOLE 200 mg – 5 times a day for 14 days in combination with other appropriate therapy.

Method of administration

Oral use.

Tablets should be swallowed without chewing, with adequate water, preferably during or after meals.

4.3 Contraindications

- Hypersensitivity to metronidazole, other imidazoles or any of the excipients listed in section 6.1.
- Patients with blood dyscrasias or with active disease of the central nervous system.
- Co-administration with busulfan (see section 4.4).

4.4 Special warnings and precautions for use

Patients should be advised not to take alcohol during BIO-METRONIDAZOLE therapy and for at least one to three days afterwards because of the possibility of a disulfiram-like reaction (see section 4.5).

Pseudomembranous colitis has been reported following the use of BIO-METRONIDAZOLE.

Studies have shown that metronidazole, as in BIO-METRONIDAZOLE, may be mutagenic in bacteria and carcinogenic in some animals.

Transient falls in blood pressure have been reported with the use of BIO-METRONIDAZOLE. It may therefore be advisable to lower the dosage of antihypertensive medicine which may be given concurrently with BIO-METRONIDAZOLE.
When repeat courses are required, leukocyte counts should be performed before, during and after each course of treatment.

All patients receiving treatment with BIO-METRONIDAZOLE for more than 10 days should be closely monitored and treatment should be discontinued if signs of peripheral neuropathy or central nervous system toxicity develop.

Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Significant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

BIO-METRONIDAZOLE should be administered with caution to patients with hepatic encephalopathy.

Due to the anti-treponemal activity of BIO-METRONIDAZOLE it may mask the immunological response seen in untreated early syphilis and contacts of syphilis treated with BIO-METRONIDAZOLE should probably be screened for an additional 4 to 8 weeks.

Patients should be warned that BIO-METRONIDAZOLE may darken urine (due to metronidazole metabolite).

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.
Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

Cases of severe bullous skin reactions such Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalised exanthematous pustulosis (AGEP) have been reported with metronidazole. If symptoms or signs of SJS, TEN or AGEP are present, BIO-METRONIDAZOLE treatment must be immediately discontinued.

There is a possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection might persist. The elimination half-life of metronidazole remains unchanged in the presence of renal failure. The dosage of BIO-METRONIDAZOLE therefore needs no reduction. Such patients however retain the metabolites of metronidazole. The clinical significance of this is not known at

present. In patients undergoing haemodialysis, metronidazole and metabolites are efficiently removed during an eight-hour period of dialysis. BIO-METRONIDAZOLE should therefore be re-administered immediately after haemodialysis.

No routine adjustment in the dosage of BIO-METRONIDAZOLE need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).

Lactose

BIO-METRONIDAZOLE contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Disulfiram

The concomitant use of BIO-METRONIDAZOLE and disulfiram has been associated with acute psychoses or confusion.

Alcohol

BIO-METRONIDAZOLE used concomitantly with alcohol may provoke a disulfiram-like reaction in some individuals (effects include intense vasodilation and flushing of the face and neck, restlessness, anxiety, tachycardia, tachypnoea, headache, nausea, vomiting, hyperpnoea, chest pains, sweating, pallor and hypotension). This reaction has occurred following the use of pharmaceutical preparations formulated with alcohol, including injections, as well as after consuming alcohol. Alcoholic beverages and medicine containing alcohol should not be consumed during therapy and for at least 1 to 3 days afterwards (see section 4.4).

Oral anticoagulant therapy (warfarin type)

BIO-METRONIDAZOLE enhances the anti-coagulant effect of warfarin and increased

haemorrhagic risk. In case of co-administration with warfarin, prothrombin time/INR should be more frequently monitored and warfarin therapy/dose adjusted during treatment with BIO-METRONIDAZOLE.

Lithium

Plasma levels of lithium may be increased by BIO-METRONIDAZOLE. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive BIO-METRONIDAZOLE.

Phenytoin or phenobarbitone

Phenytoin might accelerate the metabolism of BIO-METRONIDAZOLE.
Phenobarbitone administered concomitantly with BIO-METRONIDAZOLE causes decreased plasma concentrations of BIO-METRONIDAZOLE and thus leading to a reduction in the effectiveness of BIO-METRONIDAZOLE.

5-Fluorouracil:

Reduced clearance of 5-fluorouracil resulting in increased toxicity of 5-fluorouracil may occur.

Cimetidine

Cimetidine may increase plasma concentrations of BIO-METRONIDAZOLE and might increase the risk of neurological side effects.

Ciclosporin

The risk of elevation of serum levels of ciclosporin might be increased by BIO-METRONIDAZOLE. Serum ciclosporin and serum creatinine should be closely monitored when co-administration is necessary.

4.6 Fertility, pregnancy and lactation

The safety of BIO-METRONIDAZOLE has not been established in pregnancy and lactation.

BIO-METRONIDAZOLE crosses the placental barrier and is excreted in breast milk. Women using BIO-METRONIDAZOLE should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

BIO-METRONIDAZOLE may cause confusion, dizziness, hallucinations, convulsions or transient visual disorders and patients should be warned and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

a) Summary of the safety profile

The adverse effects of BIO-METRONIDAZOLE are generally dose related.

b) Tabulated summary of adverse reactions

Blood and lymphatic system disorders

Less frequent: Temporary moderate leucopenia, thrombocytopenia, agranulocytosis, neutropenia.

Immune system disorders

Less frequent: Anaphylaxis.

Frequency unknown: Angioedema, urticaria.

Metabolism and nutrition disorders

Frequency unknown: Anorexia.

Psychiatric disorders

Less frequent: Psychotic disorders including confusion, irritability and hallucinations,

changes in mood or mental state such as depression.

Nervous system disorders

Frequent: Vertigo (dizziness or light-headedness).

Less frequent: Weakness, drowsiness, insomnia. Peripheral neuropathy (numbness, tingling, pain, or weakness in hands or feet) has been reported with high doses or in patients on prolonged treatment; seizures – usually with high doses. Reports of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor), which may resolve with discontinuation of BIO-METRONIDAZOLE.

Eye disorders

Less frequent: Transient vision disorders such as diplopia and myopia.

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Nasal congestion.

Gastrointestinal disorders

Frequent: Gastrointestinal discomfort, nausea and unpleasant taste; vomiting and headache may accompany the nausea. Diarrhoea, dry mouth, furred tongue, oral mucositis and stomatitis may also occur.

Less frequent: Antibiotic-associated colitis, pancreatitis, pseudomembranous colitis associated with the use of BIO-METRONIDAZOLE.

Hepato-biliary disorders

Less frequent: Raised liver enzyme values (AST, ALT, alkaline phosphatase), reversible abnormal liver function and cholestatic hepatitis.

Skin and subcutaneous tissue disorder

Less frequent: Pruritus, skin rash, fever, angioedema, flushing, urticaria, anaphylaxis. Pustular eruptions may occur. Mild erythematous eruptions with fleeting joint pains resembling serum sickness.

Musculoskeletal and connective tissue disorders

Frequency unknown: Myalgia and arthralgia.

Renal and urinary disorders

Less frequent: Urethral discomfort and darkening of the urine.

General disorders and administration site conditions

Frequency unknown: Fever.

Post marketing experience

The adverse effects listed below are based on data from post-marketing experience:

Nervous system disorders: Headache, aseptic meningitis

Eye disorders: Transient vision disorders such as blurred vision, decreased visual acuity, changes in colour vision, optic neuropathy/neuritis.

Gastrointestinal disorders: Epigastric pain.

Hepato-biliary disorders: Mixed hepatitis and hepatocellular liver injury, cases of liver failure requiring liver transplant have been reported in patients treated with BIO-METRONIDAZOLE in combination with other antibiotic medicines.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BIO-METRONIDAZOLE is important. It allows continued monitoring of the benefit/risk balance of BIO-METRONIDAZOLE. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the

Adverse Drug Reactions Reporting Form, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Refer to side effects.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 20.2.6 Medicines against protozoa

Pharmacotherapeutic group: Agents against amoebiasis and other protozoal diseases, nitroimidazole derivatives. ATC code: P01A B01.

5.1 Pharmacodynamic properties

Metronidazole is active *in vitro* against a wide variety of anaerobic protozoal parasites and anaerobic bacteria. It has antiprotozoal activity against *Trichomonas vaginalis* and other protozoa, including *Entamoeba histolytica* and *Giardia lamblia*.

Metronidazole has bactericidal activity against obligate anaerobic bacteria (Gram positive and negative) and bacilli or cocci. It does not affect the acidophilic flora of the vagina. It is not effective against aerobic, facultative anaerobic bacteria as well as Candida species.

5.2 Pharmacokinetic properties

Metronidazole is completely absorbed after oral administration. The half-life of metronidazole in plasma is about 8 hours with less than 20 % of metronidazole bound to plasma proteins.

After an oral dose over 75 % of metronidazole is eliminated in the urine largely as metabolites; about 10 % is recovered as unchanged metronidazole. The liver is the main site of metabolism.

Metronidazole crosses the blood/brain barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Lactose

Magnesium stearate

Maize starch

Pregelatinised starch

Povidone.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

Do not remove the blisters from the outer carton until required for use.

6.5 Nature and contents of container

BIO-METRONIDAZOLE 200:

White PP securitainers with 250 tablets or patient ready packs (white LDPE bags) with 21 or 28 tablets.

PVC/PVDC/aluminium blisters containing 7 tablets per blister strip and 1, 2, or 3 blisters per outer carton.

BIO-METRONIDAZOLE 400:

White PP securitainers with 21, 100 or 500 tablets or patient ready packs (white LDPE bags) with 5, 14 or 21 tablets.

PVC/PVDC/aluminium blisters containing 7 tablets per blister strip and 1, 2, or 3 blisters per outer carton.

HDPE containers with caps, containing 100 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No additional information.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark

Halfway House

Midrand 1685

8. REGISTRATION NUMBERS

BIO-METRONIDAZOLE 200: V/20.2.6/0370

BIO-METRONIDAZOLE 400: V/20.2.6/0371

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 April 1989

10. DATE OF REVISION OF THE TEXT

10 June 2026