SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BEMETRAZOLE (200)

Metronidazole 200 mg (tablets)

BEMETRAZOLE (400)

Metronidazole 400 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION **BEMETRAZOLE** (200)

Each tablet contains 200 mg metronidazole.

Contains sugar: lactose monohydrate 100 mg per tablet

BEMETRAZOLE (400**)**

Each 400 mg tablet contains 400 mg metronidazole.

Contains sugar: lactose monohydrate 80 mg per tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

BEMETRAZOLE (200)

Round biconvex tablet , scored on one side

BEMETRAZOLE (400)

Round biconvex tablet , scored on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

1. In the oral treatment of:

   - Urogenital trichomoniasis.

   - Non-specific vaginitis

   - All forms of amoebiasis

   - Acute ulcerative gingivitis (Vincent's).

   - Giardiasis.

   -Acute periconitis

2. 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*.

   BEMETRAZOLE has been used successfully for anaerobicinfections in the following conditions: pelvic inflammatory disease and postoperative wound infections.

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

3. 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.

4. Treatment of *Helicobacter pylori*-associated gastritis and duodenal ulcer. **BEMETRAZOLE** is used in combination with bismuth subsalicylate or colloidal bismuth subcitrate and appropriate antibiotic therapy.

4.2 Posology and Method of Administration

Method of Administration

Tablets should be swallowed (without chewing) with half a glass of water. It is recommended that tablets be taken during or after a meal.

Children over 10 years may be given a suitable proportion of the adult dosage according to body mass

	DURATION OF DOSAGE IN DAYS	**ADULTS**	**CHILDREN**		
			7 TO 10 YEARS	**3 TO 7 YEARS**	**1 TO 3 YEARS**
UROGENITAL TRICHO-MONIASIS	1	2 g as a single dose			
. Where re-infection is likely, in adults the consort should receive a similar course of treatment	7	200 mg three times daily or 400 mg twice daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
	2	800 mg in the			

concurrentl y.		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	200 mg four times daily	200 mg three times daily
AMOEBIASIS b) Intestinal disease in less susceptible	5 to 10	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily

subjects and "chronic amoebic hepatitis".					
AMOEBIASIS c) Amoebic liver abscess, also other forms of extra-intestinal amoebiasis.	5	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 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	100 to 200 mg four times daily	100 to 200 mg three times daily
GIARDIASIS A second	3	2 g once daily	1 g once daily	600 to 800 mg once	500 mg once daily

course of treatment may be necessary for some patients two weeks after the end of the first course.				daily	
ACUTE ULCERATIVE GINGIVITIS	3	200 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
ACUTE PERICORONITIS	3 to 7	200 mg three times daily			

Anaerobic infections

a) Treatment:

Metronidazole may be given alone or concurrently with other bacteriologically-appropriate antibacterial agents. 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 and infants: 7,5 mg/kg body mass by mouth every 8 hours daily during or after meals

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.Shorter pre-operative courses and oral doses of up to 1 g have been used

Children: as for treatment (a).

Treatment of Helicobacter pylori-associated gastritis and duodenal ulcer

The following regimens have been used:

a) **BEMETRAZOLE** 200-250 mg – 4-5 times a day for 14 days in combination with other medicines.

4.3 Contraindications:

- Hypersensitivity to metronidazole and 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 metronidazole therapy and for at lea three day afterwards because of the

possibility of a disulfiram-like reaction (see section 4.5).

Co-administration with busulfan: As plasma levels of busulfan may be increased significantly, it may lead to severe busulfan toxicity and death.

Pseudomembranous colitis has been reported following the use of metronidazole.

Studies have shown metronidazole to be mutagenic in bacteria and carcinogenic in some animals.

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.

BEMETRAZOLE should be administered with caution to patients with hepatic encephalopathy.

BEMETRAZOLE should be used with great care in patients with blood dyscrasias or with active disease of the central

nervous system. All patients receiving **BEMETRAZOLE** for more than 10 days should be monitored and treatment discontinued if signs of peripheral neuropathy or CNS toxicity develop. Doses should be reduced in patients with severe liver disease.

BEMETRAZOLE has anti-treponemal activity and may mask the immunological response seen in untreated syphllis.

Contacts of syphllis receiving **BEMETRAZOLE** should be probably be screened for an

additional 4 to 8 weeks.

Patients should be warned that **BEMETRAZOLE** 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, **BEMETRAZOLE** 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 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. Metronidazole should therefore be re- administered immediately after haemodialysis.

No routine adjustment in the dosage of metronidazole need be made in patients with renal failure undergoing intermittent

peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).

Lactose:

Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medication

4.5 Interaction with other medicines and other forms of Interaction

Disulfiram:

Acute psychoses or confusion have been associated with the concomitant use of BEMETRAZOLE and disulfiram.

Alcohol:

When given in conjunction with alcohol, **BEMETRAZOLE**

may provoke a disulfiram-like reaction in some individuals (effects include intense vasodilation and flushing of the face and neck, restlessness, anxiety, tachycardia, tachypnoea, chest pains, sweating, pallour and hypotension); reactions have occurred after the administration of pharmaceutical preparations formulated with alcohol, including injections, as well as after drinking alcohol.

Alcoholic beverages and medicines 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):

Potentiation of the anticoagulant effect 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

BEMETRAZOLE

Lithium:

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

Ciclosporin:

Risk of elevation of ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when co-administration is necessary.

Phenytoin or Phenobarbitone:

There is evidence that phenytoin might accelerate the metabolism of metronidazole, as in **BEMETRAZOLE**. Plasma concentrations of metronidazole are decreased by the concomitant administration of phenobarbitone, with a consequent reduction in the effectiveness of **BEMETRAZOLE**.

5-Fluorouracil:

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

Busulfan:

Plasma levels of busulfan may be increased by **BEMETRAZOLE**, which may lead to severe busulfan toxicity and death (see section 4.4)

Cimetidine:

Hepatic metabolism may be decreased when **BEMETRAZOLE** and cimetidine are used c possibly resulting in delayed elimination and increased serum metronidazole concentrations with an increased risk of neurological side effects.

4.6 Fertility, pregnancy and lactation

The safety of use during pregnancy has not been established.

Metronidazole crosses the placental barrier and is excreted in breast milk.

Women using BEMETRAZOLE should not breastfeed their infants

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Patients should be warned about the potential for confusion,

dizziness, hallucinations, convulsions or transient visual disorders, and advised not to

drive or operate machinery if these symptoms occur

4.8 Undesirable effects

System Organ Class	**Frequent**	**Less Frequent**	**Frequency Unknown**
Blood and lymphatic system disorders		- Agranulositosis - Neutroopenia - Thrombocytopenia - Pancytopenia	- Leucopenia
Immune system disorders		- Anaphylaxis	- Angioedema - Urticaria - fever
Metabolism and nutrition disorders			- Anorexia
Psychiatric disorders		Psychotic disorders including - Confusion - Hallucination	Depressed moods

		- Irritatbility - Change in mood or mental state such as depression or confusion	
Nervous system disorders		- Weakness - Dizziness - Drowsiness - Insomnia - cases of encephelopather (eg confusion) and subacute cerebellar syndrome(eg ataxia,dysarthria, gait impairment,nystagmus and tremor which may resolve with discontinuation of BEMETRAZOLE - headache	-Peripheral Neuropathy usually presenting as numbness or tingling in extremeties - Epileptiform seizures - Aseptic meningitis - headache
Eye disorders	-	- Transient vision disorders such as Diplopia and myopia	-Optic neuropathy/neuritis -Transient vision disorders such as blurred vision, decreased visual acuity, changes in colour vision

Ear and Labyrinth disorders	-	-	Hearing impaired/hearing loss(including sensorineural) ,tininitus
Respiratory, thoracic and mediastinal disorders			- Nasal congestion
Gastrointestinal disorders	gasstrointestinal disturbances, especially nausea and taste disorders; nausea is sometimes accompanied by headache, and vomiting. -Diarrhoea -dry mouth, -a furred tongue - oral mucositis -stomatitis	pseudomembranous colitis	-Epigastric pain

Hepatobiliary disorders		- Increase in liver enzymes - cholestatic hepatitis sometimes with jaundice	-Pancreatitis -Raised liver enzyme values -Mixed hepatitis and hepatocellular liver injury -jaundice and pancreatic which is reversible on drug withdrawal
Skin and subcutaneous tissue disorders		**-**Pastular eruptions -Mild erythemous eruptions with fleeting joint pains resembling serum sickness	-Skin rashes -Fever -Flushing -Puritis -Erythema Multiforma -Steven Johnson syndrome -Toxic Epidermal Necrosis

Musculoskeletal and connective tissue disorders			- Arthralgia - Myalgia
Renal and urinary disorders		- Urinary discomfort - Darkening of urine	
General disorders and administration site conditions:			**-**Fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the

medicine is important. It allows continued monitoring of the benefit/risk balance of the me

Healthcare professionals are asked to report any suspected adverse reactions to SAHPR

"6.04 Adverse Drug Reaction" Reporting Form", found online under SAHPRA's

publications:

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

4.9 Overdose

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Category and class: A 20.2.6 Antimicrobial (chemotherapeutic) agents: Medicines against protozoa

ATC code: P01A B01

Mechanism of action

Metronidazole has antiprotozoal activity against *Trichomonas vaginalis* and other protozoa, including *Entamoeba histolytica* and *Giardia lamblia.* It does not affect the acidophilic flora of the vagina and it has no effect on Candida species. Metronidazole has bactericidal activity against obligate anaerobic bacteria, whether they are Gram-positive or –negative and bacilli or cocci.

It has no antibacterial activity against aerobic and facultative anaerobic bacteria. Metronidazole does not interfere with the activity of antibacterial medicines which are active against a variety of aerobes and facultative anaerobes.

The following has been proposed as the mode of action of metronidazole: The parent compound penetrates the cell membrane unchanged, but once inside the cell the nitro group is reduced in the redox conditions prevalent in the anaerobic cell. The reduced product is known to damage DNA causing eventual death of the organism.

5.2 Pharmacokinetic properties:

Absorption

Metronidazole is absorbed from the gastrointestinal tract

Distribution

It is widely distributed in body tissues. Metronidazole is able to pass the blood-brain

barrier. It reaches therapeutic concentrations in most other body fluids, i.e. saliva, bile, urine, amniotic fluid, breast milk and in abscess cavities

Biotransformation

Approximately 30-40 % of a dose is metabolised in the liver

Elimination

It is excreted in the urine, together with the unchanged compound. Metronidazole is able t blood-brain barrier. It reaches therapeutic concentrations in most other body fluids, i.e. sa urine, amniotic fluid, breast milk and in abscess cavities

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate 200, magnesium stearate, pregelatinized starch, purified talc starch maize,

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months: **BEMETRAZOLE** (200) : tablets are packed in securitainers in 21's,100's or 500's

24 Months: BEMETRAZOLE (400):tablets are packed in securitainers in 10's,100's or 500's as well as 500's in HDPE containers

15 months: Patient ready packs of different pack sizes

6.4 Special precautions for storage

Store at or below 25 ^{0}C.

Store out of direct sunlight

6.5 Nature and contents of container

BEMETRAZOLE (200) : tablets are packed in securitainers in 21's,100's or 500's

Patient ready packs of different pack sizes.

BEMETRAZOLE (400) : tablets are packed in securitainers in 10's,100's or 500's as well as 500's in HDPE containers

Patient ready packs of different pack sizes.

6.2 Special precautions for disposal

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispc unused medicines in drains or sewage systems

(e.g. toilets)

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext. 1

Roodepoort

1724

South Africa

REGISTRATION NUMBER(S)

South Africa

BEMETRAZOLE (200): 29/20.2.6/0745

BEMETRAZOLE (400): X/20.2.6/64

Namibia:

BEMETRAZOLE (200) NS2 Reg. No.: 04/20.2.6/0097 (500's)

BEMETRAZOLE (400) NS2 Reg. No.: 90/20.2.6/00362

(10's;100's & 500's)

Botswana:

Botswana List No.: B9314815 for Bemetrazole 400 mg (100`s & 500`s

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

BEMETRAZOLE (200) : 24 May 1996

BEMETRAZOLE (400) : 28 September 1989

10.DATE OF REVISON OF THE TEXT

13 January 2022