SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

METRAZOLE, 400 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg metronidazole.

Contains sugar as 80 mg lactose per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Yellow, round, flat tablet, scored on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

A. In the oral treatment of:

- Urogenital trichomoniasis
- All forms of amoebiasis except asymptomatic carrier state
- Acute ulcerative gingivitis (Vincent's)
- Giardiasis
- Non-specific vaginitis

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.

METRAZOLE 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 postoperative infections due to anaerobic bacteria:

- Given before and after gynaecological surgery.
- Given before and after appendectomy.
- Given before and after colonic surgery.

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

4.2 Posology and method of administration

Posology

The tablets should be taken orally.

Adults and adolescent (over 12 years)

Indications	**Duration of dosage in days**	**Number of tablets to be taken**

UROGENITAL TRICHOMONIASIS: Where re-infection is likely, the consort should receive a similar course of treatment concurrently	7 or	1 tablet (400 mg) twice a day
	2 or	2 tablets (800 mg) in the morning and 3 tablets (1 200 mg) in the evening
	1	5 tablets (2 000 mg) as a single dose
AMOEBIASIS: a) Intestinal disease in susceptible subjects	5	2 tablets (800 mg) three times a day
b) Intestinal disease in less susceptible subjects and chronic amoebic hepatitis	5 to 10	1 tablet (400 mg) three times a day
c) Amoebic liver abscess also other forms of extra-intestinal amoebiasis	5	1 tablet (400 mg) three times a day
d) Symptomless cyst passers	5 to 10	1 tablet (400 mg) to 2 tablets (800 mg) three times a day
ACUTE ULCERATIVE GINGIVITIS	3	1 tablet (400 mg) twice a day
GIARDIASIS: A second course of treatment may be necessary for some	3	5 tablets (2 000 mg) once a day

patients two weeks after the end of the first course.		
NON-SPECIFIC VAGINITIS	7 or	1 tablet (400 mg) twice a day
	1	5 tablets (2 000 mg) once a day

ANAEROBIC INFECTIONS

a) Treatment

METRAZOLE tablets may be given alone or concurrently with other bacteriologically appropriate anti-bacterial agents. They should be given for 7 days or longer depending on clinical and bacteriological assessment of the patient's condition.

Adults: 400 mg by mouth three times daily during or after meals.

Children: Children who can swallow tablets 7,5 mg/kg three times daily.

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: Children who can swallow tablets 7,5 mg/kg three times daily.

Special populations

See section 4.4.

Paediatric population

Children weighing less than 10 kg should receive more appropriate dosage strengths and forms. Children over 10 years may be given a suitable proportion of the adult dosage according to their body mass.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to metronidazole, other imidazoles or to any of the excipients (see section 6.1)
- Patients with blood dyscrasias or with active disease of the central nervous system.
- Its use should be avoided during pregnancy.
- Co-administration with busulfan (see sections 4.4 and 4.5)

4.4 Special warnings and precautions for use

Alcohol

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

Oral anticoagulants

METRAZOLE enhances the effect of warfarin and when given to patients receiving warfarin or other oral anticoagulants, the dosage of the latter should be recalibrated (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 (see sections 4.3 and 4.5).

Pseudomembranous colitis

Pseudomembranous colitis has been reported following the use of METRAZOLE.

Blood pressure

Slight and transient falls in blood pressure have been reported with the parent substance; it may therefore be advisable to lower the dosage of any antihypertensive drug which may be given concurrently with the tablets (see section 4.5).

Bone marrow depression and peripheral neuropathy

During intensive and prolonged treatment bone marrow depression and peripheral neuropathy have been reported. Side effects are more prominent with larger doses (see section 4.8).

All patients receiving METRAZOLE for more than 10 days should be monitored and treatment discontinued if signs of peripheral neuropathy or central nervous system toxicity (such as paraesthesia, ataxia, dizziness, vertigo, convulsive seizures) develop.

Anti-treponemal activity

METRAZOLE has anti-treponemal activity and may mask the immunological response seen in untreated early syphilis; contacts of syphilis receiving METRAZOLE should probably be screened for an additional 4 to 8 weeks.

Darken urine

Patients should be warned that METRAZOLE may darken urine (due to metronidazole metabolite) (see section 4.8).

Hepatic insufficiency

Metronidazole as in METRAZOLE is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Using METRAZOLE to treat trichomoniasis in such patients should be carefully considered.

Hepatic encephalopathy

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

Hepatotoxicity in patients with Cockayne Syndrome

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 as in METRAZOLE for systemic use. In this population, METRAZOLE should therefore be used if no alternative treatment is available. Liver function tests must be performed just prior to the start of the 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, METRAZOLE 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.

Liver failure

Cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole mostly when used in combination with other antibiotic medicines.

Severe bullous skin reaction

Cases of severe bullous skin reaction such as Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalized exanthematous pustulosis (AGEP) have been reported with metronidazole (see section 4.8). If symptoms or signs of SJS, TEN or AGEP are present, METRAZOLE treatment must be immediately discontinued.

Laboratory tests results

Metronidazole as in METRAZOLE may interfere with certain types of blood test determinations in blood (aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), triglycerides, glucose), which may lead to false negative or an abnormally low result. These analytical determinations are based on a decrease in ultraviolet absorbance, a fact that occurs when nicotinamide adenine dinucleotide hydrogen (NADH) is oxidized to nicotinamide adenine dinucleotide (NAD). The interference is due to the similarity in the absorption peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Excipients with known effect

METRAZOLE contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take METRAZOLE.

Special populations

Elderly

No information is available on the relationship of age to the effects of METRAZOLE in elderly patients. However, elderly patients are more likely to have an age-related decrease in hepatic function, which may require an adjustment in dosage.

Hepatic impairment

Dose should be reduced in patients with severe liver disease.

Renal impairment

Adjustment of dosage does not appear necessary in patients with renal impairment. Metronidazole as in METRAZOLE is removed during haemodialysis and should be administered after the procedure is finished.

4.5 Interactions with other medicines and other forms of interaction

Alcohol

It is recommended that METRAZOLE not be used concurrently with, or for at least 3 days following, ingestion of alcohol; accumulation of acetaldehyde by interference with the oxidation of alcohol may occur, resulting in disulfiram-like effect such as abdominal cramps, nausea, vomiting, headache, or flushing; in addition, modifications in the taste of alcoholic beverages have been reported during concurrent use.

Anticoagulants, coumarin- or indandione-derivative

Effects of anticoagulants may be potentiated when these agents are used concurrently with METRAZOLE, because of inhibition of enzymatic metabolism of anticoagulants; periodic prothrombin time determinations may be required during therapy to determine if dosage adjustments of anticoagulants are necessary.

Cimetidine

Hepatic metabolism of metronidazole may be decreased when METRAZOLE and cimetidine are used concurrently, possibly resulting in delayed elimination and increased serum metronidazole concentrations; monitoring of serum concentrations as a guide to dosage is recommended since dosage adjustments of METRAZOLE may be necessary during and after cimetidine therapy.

Disulfiram

It is recommended that METRAZOLE not be used concurrently with, or for 2 weeks following disulfiram in alcoholic patients, such use may result in confusion and psychotic reactions because of combined toxicity.

Lithium

Lithium concentrations may increase when METRAZOLE therapy is introduced; serum lithium and serum creatinine levels should be monitored several days after beginning METRAZOLE in order to detect impending lithium intoxication.

Neurotoxic medications

Concurrent use of METRAZOLE with other neurotoxic medications may increase the potential for neurotoxicity.

Phenobarbital

Phenobarbital may induce microsomal liver enzymes, increasing METRAZOLE's metabolism and resulting in a decrease in half-life and plasma concentration.

Phenytoin

METRAZOLE may impair the clearance of phenytoin, increasing phenytoin's plasma concentration.

Busulfan

Co-administration of METRAZOLE and busulfan is contraindicated (see section 4.3). METRAZOLE may increase plasma levels of busulfan significantly and it may lead to severe busulfan toxicity and death (see section 4.4).

Ciclosporin

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

5-Fluorouracil

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

Medicines that prolong QT interval

QT prolongation has been reported, particularly when METRAZOLE was administered with medicines with the potential for prolonging the QT interval.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy have not been established. METRAZOLE should not be used during pregnancy (see section 4.3).

Teratogenicity has been demonstrated in animal studies.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

It is not always possible to predict to what extent METRAZOLE may interfere with the daily activities of a patient. Patients should be warned about the potential for drowsiness, dizziness, confusion, hallucinations, convulsions or transient visual disorders (see section 4.8), and be advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, neutropenia, thrombocytopenia
	Frequency unknown	Leukopenia
Immune system disorders	Less frequent	Hypersensitivity (e.g. skin rash, hives, redness or itching), anaphylaxis
	Frequency unknown	Angioedema
Metabolism and nutrition disorders	Less frequent	Anorexia
Psychiatric disorders	Less frequent	Psychotic disorders, including confusion, irritability, and hallucinations changes in mood or mental state such as depression or confusion
Nervous system disorders	Less frequent	Ataxia, encephalopathy, headache, dizziness or light headedness, seizures, insomnia, subacute cerebellar syndrome (e.g. ataxia dysarthria, gait impairment, nystagmus and tremor), which may resolve with discontinuation of the medicine
	Frequency unknown	Peripheral neuropathy, aseptic meningitis

System Organ Class	Frequency	Adverse reactions
Eye disorders	Less frequent	Transient vision disorders such as diplopia and myopia
	Frequency unknown	Transient vision disorders such as blurred vision, decreased visual acuity, changes in colour vision, optic neuropathy/neuritis
Ear and labyrinth disorders	Frequency unknown	Hearing impaired/hearing loss (including sensorineural), tinnitus
Cardiac disorders	Frequency unknown	QT prolongation has been reported, particularly when METRAZOLE was administered with medicines with the potential for prolonging the QT interval
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Nasal congestion
Gastrointestinal disorders	Frequent	Dry mouth, unpleasant metallic taste, diarrhoea, nausea or vomiting, stomach pain or cramps, furred tongue, oral mucositis, stomatitis
	Less frequent	Pseudomembranous colitis
	Frequency unknown	Epigastric pain

System Organ Class	Frequency	Adverse reactions
Hepato-biliary disorders	Less frequent	Increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, jaundice, pancreatitis
Skin and subcutaneous tissue disorders	Less frequent	Pustular eruptions, mild erythematous eruptions with fleeting joint pains resembling serum sickness
	Frequency unknown	Skin rashes, flushing, and pruritus, urticaria, acute generalised exanthematous pustulosis, fixed drug eruption, Stevens-Johnson syndrome, toxic epidermal necrolysis.
Musculoskeletal, connective tissue and bone disorders	Less frequent	Myalgia, arthralgia
Renal and urinary disorders	Less frequent	Dark urine, dysuria, cystitis, sense of pelvic pressure.
General disorders and administrative site conditions	Frequency unknown	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 medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

In addition, side-effects can also be reported to info@pharmacorp.co.za.

4.9 Overdose

It is documented that in an accidental overdose of up to 12 g, symptoms were vomiting, ataxia and slight disorientation (see section 4.8). There is no specific treatment for gross overdosage and in cases of suspected massive overdosage, a symptomatic and supportive treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 20.2.6 Medicines against protozoa.

Pharmacotherapeutic group: Antibacterials for systemic use

ATC code: J01XD01

Metronidazole has anti-protozoal activity and is effective against *Trichomonas vaginalis* and other protozoa, including *Entamoeba histolytica* and *Giardia intestinalis*.

It does not affect the acidophilic flora of the vagina and it has no effect on Candida species.

Metronidazole has bactericidal activity against 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 agents 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 well absorbed from the gastro-intestinal tract and widely distributed in body tissues. It has a bioavailability of at least 80 %.

Distribution

Metronidazole is distributed to saliva, bile, seminal fluid, breast milk, bone, liver and liver abscesses, lungs and vaginal secretions; crosses the placenta and blood-brain barrier also.

Volume of distribution

In adults: Approximately 0,55 L/kg

In neonates: 0,54 – 0,81 L/kg

Protein binding

Low (< 20 %)

Biotransformation

Hepatic: Metabolised primarily by side-chain oxidation and glucuronide conjugation to 2-hydroxymethyl (also active) and other metabolites.

Half-life

In adults: Normal liver function: 8 hours (range, 6 to 12 hours).

Alcoholic liver disease: 18 hours (range, 10 to 29 hours).

In neonates: 28 to 30 weeks gestational age: Approximately 75 hours.

32 to 35 weeks gestational age: Approximately 35 hours.

36 to 40 weeks gestational age: Approximately 25 hours.

Time to peak serum concentration

1 to 2 hours (oral).

Peak serum concentration

Peak serum concentrations following a 250 mg, 500 mg and 2 g oral dose are approximately 6, 12 and 40 µg/mL respectively. All recommended intravenous doses, peak steady-state serum concentrations are approximately 25 µg/mL; through concentrations are approximately 18 µg/mL.

Elimination

Renal: 60 % to 80 % of this amount, approximately 20 % excreted unchanged in urine. Renal clearance approximately 10 mL/min/1,73 m^2.

Faecal: 6 % to 15 % inactive metabolites are also present in faeces.

In dialysis

Haemodialysis: Metronidazole and primary metabolites rapidly removed from the blood by haemodialysis (half-life shortened to approximately 2,6 hours).

Peritoneal dialysis: Metronidazole is not significantly removed by peritoneal dialysis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Magnesium stearate (E572)

Quinoline yellow (C.I. 47005) (E104)

Starch, maize (E1404)

Starch, pregelatinised (E1422)

Talc (E553b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool place (at or below 25 °C) out of direct sunlight.

6.5 Nature and contents of container

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharmacorp (Pty) Ltd

29 Victoria Link

Route 21 Corporate Park

Irene, 0178, RSA

8. REGISTRATION NUMBER

S/20.2.6/251

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

16 September 2005

10. DATE OF REVISION OF THE TEXT: 08 August 2025