Package insert

SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

METRONIDAZOLE 200 UNIMED (Tablets)

METRONIDAZOLE 400 UNIMED (Tablets)

COMPOSITION:

Each **METRONIDAZOLE 200 UNIMED** tablet contains 200 mg metronidazole.

Each **METRONIDAZOLE 400 UNIMED** tablet contains 400 mg metronidazole.

Excipients: dibasic calcium phosphate, crospovidone, magnesium stearate, maize starch, and povidone (polyvinylpyrrolidone K25).

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.6 Antimicrobials (chemotherapeutic agents): Medicines against protozoa

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties:

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 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.

Pharmacokinetic Properties:

Metronidazole is absorbed from the gastro-intestinal tract and widely distributed in body tissues. Approximately 30 – 40 % of a dose is metabolised in the liver and excreted in the urine, together with the unchanged compound. 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.

INDICATIONS:

a) **METRONIDAZOLE UNIMED** is indicated in the oral treatment of:

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

It has been used successfully for anaerobic infections in the following conditions: pelvic inflammatory disease and post-operative 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. It is used in combination with bismuth subsalicylate or colloidol bismuth subcitrate and appropriate antibiotic therapy.

CONTRAINDICATIONS:

Hypersensitivity to metronidazole and other imidazoles or any of the excipients used in **METRONIDAZOLE UNIMED**.

Co-administration with busulfan **(see WARNINGS AND SPECIAL PRECAUTIONS AND INTERACTIONS).**

WARNINGS and SPECIAL PRECAUTIONS:

Patients should be advised not to take alcohol during **METRONIDAZOLE UNIMED** therapy and for at least one day afterwards because of the possibility of a disulfiram-like reaction **(see INTERACTIONS).**

Pseudomembranous colitis has been reported with the use of **METRONIDAZOLE UNIMED**.

METRONIDAZOLE UNIMED should be used with great care in patients with blood dyscrasias or with active or chronic disease of the central and peripheral nervous system.

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

Co-administration of **METRONIDAZOLE UNIMED** with Busulfan: Plasma levels of busulfan may be increased significantly which may lead to severe busulfan toxicity and death **(see CONTRAINDICATIONS AND INTERACTIONS).**

METRONIDAZOLE UNIMED has anti-treponemal activity and may mask the immunological response seen in untreated early syphilis; contacts of syphilis receiving **METRONIDAZOLE UNIMED** should be screened for an additional 4 to 8 weeks.
Patients should be warned that **METRONIDAZOLE UNIMED** may darken urine (due to metronidazole metabolite).

Effects on ability to drive and use machinery:

Patients should be warned about the potential for confusion, dizziness, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate heavy machinery if these symptoms occur.

INTERACTIONS:

Disulfiram:

Acute psychoses or confusion have been associated with the concomitant use of **METRONIDAZOLE UNIMED** and disulfiram.

Alcohol:

When given in conjunction with alcohol **METRONIDAZOLE UNIMED** 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, pallour and hypotension); reactions have occurred after the administration of pharmaceutical preparations formulated with alcohol, including injections, as well as after drinking alcohol.

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 **METRONIDAZOLE UNIMED.**

Lithium:

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

Ciclosporin:

Risk of elevation ciclosporin serum levels. Serum ciclosprin 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 UNIMED.** Plasma concentrations of **METRONIDAZOLE UNIMED** are decreased by the concomitant administration of phenobarbitone, with a consequent reduction in the effectiveness of **METRONIDAZOLE UNIMED.**

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 **METRONIDAZOLE UNIMED,** which may lead to severe busulfan toxicity and death **(see CONTRAINDICATIONS AND WARNINGS AND SPECIAL PRECAUTIONS).**

Cimetidine:

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

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

METRONIDAZOLE UNIMED crosses the placental barrier and is excreted in breast milk.

Use in pregnancy and lactation should be carefully evaluated.

DOSAGE AND DIRECTIONS FOR USE:

The tablets should be taken with or after food.

	Duration of Dosage in days	ADULTS	CHILDREN	
			7 to 10 years	3 to 7 years
UROGENITAL TRICHOMONIASIS Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently.	1	2 g as a single dose		
	7	200 mg three times daily or 400 mg twice daily	100 mg three times daily	100 mg twice daily
	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	200 mg four 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	100 mg four times daily
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
AMOEBIASIS d) Symptomless cyst passers.	5 to 10	400 mg to 800 mg three times daily	200 mg to 400 mg three times daily	100 to 200 mg four 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	600 mg to 800 mg once daily
ACUTE ULCERATIVE GINGIVITIS	3	200 mg three times daily	100 mg three times daily	100 mg twice daily
ACUTE PERICORONITIS	3 to 7	200 mg three times daily		

Anaerobic infections

a) **Treatment:**

METRONIDAZOLE UNIMED tablets 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: 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

The following regimens have been used:

a) Colloidal bismuth subcitrate 108 mg, tetracycline HCℓ 500 mg, 250 mg of **METRONIDAZOLE UNIMED** – 4 times a day for 14 days.

b) Colloidal bismuth subcitrate 108 mg, tetracycline HCℓ 250 mg**, METRONIDAZOLE 200 UNIMED** mg – 5 times a day for 14 days.

SIDE-EFFECTS:

The adverse effects of METRONIDAZOLE UNIMED are generally dose related.

Gastrointestinal disorders:

Frequent: Gastrointestinal disturbances, especially nausea and taste disorders; nausea is sometimes accompanied by headache, anorexia and vomiting. Diarrhoea, dry mouth, a furred tongue, oral mucositis and stomatitis may also occur.

Less frequent: Antibiotic-associated colitis has been reported.

The following side-effect has been reported and frequency is unknown:

Pseudomembranous colitis has been reported with the use of **METRONIDAZOLE UNIMED**.

Psychiatric disorders:

Less frequent: Psychotic disorders, including confusion, irritability and hallucinations, changes in mood or mental state such as depression have been reported.

Nervous system disorders:

The following side-effects have been reported and frequencies are unknown: Peripheral neuropathy, usually presenting as numbness or tingling in the extremities, and epileptiform seizures are serious adverse effects on the nervous system that have been associated especially with high doses of **METRONIDAZOLE UNIMED** or prolonged treatment.

Less frequent: Convulsions, headache, weakness, dizziness, drowsiness, insomnia, reports of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g.ataxia dysathria, gait impairment, nystagmus and tremor), which may resolve with discontinuation of **METRONIDAZOLE UNIMED.**

Blood and lymphatic system disorders:

The following side-effects have been reported and frequencies are unknown: Temporary moderate leucopenia may occur in some patients receiving **METRONIDAZOLE UNIMED.**

Less frequent: Cases of agranulocytosis, neutropenia and thrombocytopenia, pancytopenia have been reported.

Immune system disorders:

The following side-effects have been reported and frequencies are unknown: Angioedema.

Less frequent: Anaphylaxis has been reported.

Skin and subcutaneous disorders:

The following side-effects have been reported and frequencies are unknown: Skin rashes, fever, flushing, urticaria and pruritus, occur occasionally.

Less frequent: Pustular eruptions may occur. Mild erythematous eruptions with fleeting joint pains resembling serum sickness.

Musculoskeletal, connective tissue and bone disorders:

The following side-effects have been reported and frequencies are unknown: Myalgia and arthralgia.

Eye disorders:

Less frequent: The occurrence of transient vision disorders such as diplopia and myopia may follow the use of **METRONIDAZOLE UNIMED.**

Respiratory, thoracic and mediastinal disorders:

The following side-effect has been reported and frequency is unknown: Nasal congestion.

Hepato-biliary disorders:

Less frequent: Cases of reversible abnormal liver function and cholestatic hepatitis with jaundice have been reported.

The following side-effects have been reported and frequencies are unknown: pancreatitis and raised liver enzyme values have occasionally been reported.

Renal and urinary disorders:

Less frequent: Urethral discomfort and darkening of the urine.

Other:

The following side-effects have been reported and frequencies are unknown: Studies have shown **METRONIDAZOLE UNIMED** to be mutagenic in bacteria and carcinogenic in some animals.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See "**SIDE-EFFECTS**" above.

Treatment is symptomatic and supportive.

IDENTIFICATION:

METRONIDAZOLE 200 UNIMED Tablets: White or creamy white tablets with breakline on one side and plain on the other side.

METRONIDAZOLE 400 UNIMED Tablets: Flat, white, bevelled edge tablets, scored on one side and marked MP36 on the other side.

PRESENTATION:

METRONIDAZOLE 200 UNIMED Tablets are available as:

1. Opaque PVC / Aluminium foil blister [with VMCH (copolymer of vinyl chloride and vinyl acetate) heat seal coating] strips containing 7 or 10 tablets. Two, three or four blister strips are packed in a carton, or
2. White, round HDPE container with white Polypropylene (PP) cap in a pack size of 100 or 250 tablets.

METRONIDAZOLE 400 UNIMED Tablets are available as:

1. Opaque PVC / Aluminium foil blister [with VMCH (copolymer of vinyl chloride and vinyl acetate) heat seal coating] strips containing 5, 7 or 10 tablets. One, two or three blister strips are packed in a carton. or
2. White, round HDPE container with white Polypropylene (PP) cap in a pack size of 100 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Protect from light.

Do not remove the blister from the carton until required for use.

The HDPE containers must be kept tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

METRONIDAZOLE 200 UNIMED Tablets 45/20.2.6/0828

METRONIDAZOLE 400 UNIMED Tablets 45/20.2.6/0829

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Unimed Healthcare (Pty) Ltd

Cnr. Birch Road & Bluegum Avenue

Anchorville, Lenasia, 1827

South Africa

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