

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metronide 400mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400mg Metronidazole.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, circular, biconvex tablets, 12.5mm in diameter with a single breakline and 'MZL 400' on one face and a twin triangle logo on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of urogenital trichomoniasis.

In the treatment of acute ulcerative gingivitis.

In the treatment of infections due to *Entamoeba histolytica* (including carrier states).

In the treatment of infections due to *Giardia lamblia* (including carrier states).

In the prevention and treatment of infections due to anaerobic bacteria, particularly species of Bacteroides, anaerobic streptococci, fusobacteria, clostridia, etc.

In the treatment of acute dental infections.

In the treatment of chronic pressure sores and ulcers with possible anaerobic infection.

In the treatment of non-specific vaginitis.

4.2 Posology and method of administration

Urogenital Trichomoniasis

Adults and children over 10 years:

600mg daily in divided doses for 7 days. (Where appropriate the partner should be treated at the same time).

A short two day course of 2g in 2 divided doses daily may be used, or a single dose of 2g.

Children:

- Aged 7-10 years: 300mg daily in three divided doses.
Aged 3-7 years: 200mg daily in two divided doses.
Aged 1-3 years: 150mg daily in 3 divided doses.
Treatment should continue for 7 days.

Acute Ulcerative Gingivitis

Adults and children over 10 years:

600mg in divided doses for 3 days.

Children:

- Aged 7-10 years: 300mg daily in three divided doses for 3 days.
Aged 3-7 years: 200mg daily in two divided doses for 3 days.
Aged 1-3 years: 150mg daily in three divided doses for 3 days.

Amoebiasis

Adults and children over 10 years

1,200 – 2,400mg daily in three divided doses.

Children:

- Aged 7-10 years: 600 – 1,200mg daily in three divided doses.
Aged 3-7 years: 400 – 800mg daily in four divided doses.
Aged 1-3 years: 300 – 600mg daily in three divided doses.

Treatment is usually required for 5 to 10 days.

Giardiasis

Adults and children over 10 years:

2000mg once daily for 3 days.

Children:

- Aged 7-10 years: 1,000mg once daily for 3 days.
Aged 3-7 years: 600mg daily for 3 days.
Aged 1-3 years: 400-500mg once daily for 3 days.

Anaerobic Infections

Adults:

800mg followed by 400mg 8 hourly.

Children:

7.5mg/Kg three times daily.

Treatment should be continued as indicated by the clinical and bacteriological assessment by the clinician. Seven days should generally be sufficient.

Prophylaxis against Anaerobic infections:

Adults:

400mg at 8 hourly intervals during the 24 hours immediately preceding operation, followed post operatively by intravenous or rectal administration until oral dosing can be resumed.

Children :

7.5mg/kg 8 hourly.

Please refer to local hospital infection control guidelines. The prophylactic treatment may only be required for 24 hours. The strategy used should minimize the potential for development of antibiotic organisms.

Dental Infections

The usual totally daily dosage is 600 – 800mg in divided doses. Treatment should generally be continued for 3-7 days.

Chronic pressure sores and ulcers

Adults:

1,200mg daily in three divided doses.

Non-specific vaginitis

Adults and children over 10 years:

A single dose of 2g may be used or 400mg twice daily for 7 days.

These tablets should be swallowed with water and taken during or after a meal.

Adjustment of dosage does not appear to be necessary in patients with renal impairment.

In cases of children whose weights are below those usual for their age, or for infants below 10kg in weight, dosage should be reduced proportionately.

Elderly:

Caution is advised particularly at high doses. No information is available on modification of dosage.

Hepatic Encephalopathy

Daily dosage should be reduced to one third and may be given once daily (*see section 4.4, Special warnings and precautions for use*).

Route of administration

Oral.

4.3 Contraindications

Use in patients with known hypersensitivity to metronidazole.

Use in patients with central or peripheral disease of the nervous system.

4.4 Special warnings and precautions for use

If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible. High dosage regimens have been associated with transient epileptiform seizures. Caution is required in patients with active disease of the central nervous system except for brain abscess. Regular clinical and laboratory monitoring is advised if administration of metronidazole for more than 10 days is considered necessary.

Metronidazole and its metabolites have been shown to be mutagenic in some tests with non-mammalian cells.

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. This product should therefore be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

The elimination half-life of metronidazole remains unchanged in the presence of renal failure and therefore no reduction in dosage is necessary. Such patients retain the metabolites of metronidazole. As metronidazole and its metabolites are removed during haemodialysis, it should be readministered after the procedure is finished.

Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and are under specialist direction.

There is a possibility that after *Trichomonas vaginalis* has been eliminated, a gonococcal infection might persist.

Aspartate amino transferase assays may give spuriously low values in patients taking metronidazole depending on the method used.

This product contains Lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should be advised not to take alcohol during metronidazole therapy and for a least 48 hours afterwards because of the possibility of a disulfiram-like (antabuse effect) i.e. nausea, vomiting, headaches, flushing and high blood pressure.

Potential of coumarin anticoagulant effects may occur with metronidazole, and anticoagulant activity should be carefully monitored during concurrent therapy.

Patients receiving phenobarbitone metabolise metronidazole at a much greater rate than normal, reducing the half life to approximately 3 hours. A similar effect may occur with other drugs which induce hepatic microsomal enzymes.

Cimetidine prolongs the half life of metronidazole.

Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and metronidazole. Lithium treatment should be tapered or withdrawn before administering metronidazole. Plasma concentration of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Ciclosporin: risk of elevation of the ciclosporin serum levels. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Flurouracil: reduced clearance of 5 fluorouracil resulting in increased toxicity of 5 fluorouracil.

4.6 Pregnancy and lactation

Metronidazole should only be used during pregnancy or lactation if considered essential by the physician. Studies in animals have shown no teratogenic effect. If used, high dosage regimes should be avoided. The drug crosses the placenta and is excreted in breast milk in concentrations equal to those in serum.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Gastrointestinal effects

- epigastric pain, nausea, vomiting, diarrhoea
- glossitis, metallic taste, dry mouth, anorexia
- Pancreatitis

Hypersensitivity reactions

- rash, pruritus, flushing, urticaria
- fever, angioedema, anaphylactic shock

Peripheral and central nervous System

- peripheral sensory neuropathy
- headache, convulsions, dizziness, ataxia

Psychiatric disorders

- confusion, hallucinations

Haematology

- very rare cases of agranulocytosis, neutropenia and thrombocytopenia have been reported.

Liver

- very rare cases of abnormal liver function tests and cholestatic hepatitis have been reported.

4.9 Overdose

One case report of a voluntary overdose of 4,200mg in a 16-year-old pregnant woman reported that the patient developed disorientation, which resolved without specific treatment. Larger doses than this reported overdose have been given to patient as a radiosensitizer without severe toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Classification: J01XD01

Pharmacotheapeutic Group: Antibacterials, Imidazole Derivatives.

Metronidazole is an antimicrobial drug that is primarily active against obligate anaerobic microorganisms, both bacteria and protozoa. The 5-nitro-group undergoes reductive transformation to an active intermediate, which then exerts an inhibitory or lethal effect against DNA. Not only is DNA synthesis inhibited but the reduced metabolite also causes a loss of helical structure of DNA with subsequent DNA strand breakage. The structure of the intermediate has not been determined. Other reduction-oxidation processes within anaerobic organisms may also be inhibited (for example, the phosphorclastic reaction in clostridia), which also contributes to cell death. In vitro, metronidazole demonstrates a consistently rapid bactericidal effect with the minimal bactericidal concentration approximating very closely to the minimal inhibitory concentration.

5.2 Pharmacokinetic properties

The bioavailability of oral metronidazole approaches 90 –100%. Peak serum levels of metronidazole after a single 500mg oral dose range between 9 and 13 mg/l.⁻¹ and occur 0.33 to 3 hours after the dose. With multiple oral doses, there is some drug accumulation, with minimum serum levels averaging 17 mg.l.⁻¹ on day 3 on a dose of 500mg 6-hourly with no evidence of further accumulation by day 7. On a multiple dose regimen of 250mg 8-hourly, minimum serum levels were approximately 4mg.l.⁻¹. Serum levels are directly proportional to the dose over a broad therapeutic range.

Pharmacokinetic parameters have been derived from several studies in which serum concentration/time data from intravenous infusions of metronidazole were analysed. There is considerable variation in these parameters among individual patients or volunteers.

Oral absorption	90 - 100%
Presystmeic metabolism	negligible
Plasma half life range	7.9 - 9.8 h
Volume of distribution	0.76 -1.02 l.kg ⁻¹
Plasma protein binding	0 - 20%

5.3 Preclinical safety data

No information submitted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
 Maize starch
 Povidone
 Magnesium stearate
 Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep blister in outer carton.
Store in the original package.

6.5 Nature and contents of container

250 µm/60g/m² PVC/PVdC and 20 µm aluminium foil blisters contained in a carton.

Pack sizes: 14, 100, 250, 500 and 1000 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited,
Waterford Road,
Clonmel,
County Tipperary.

8 MARKETING AUTHORISATION NUMBER

PA 0126/056/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 February 1985

Date of last renewal: 01 February 2005

10 DATE OF REVISION OF THE TEXT

March 2008