1. Product Name

Metrogyl 200 mg and 400 mg tablets.

2. Qualitative and Quantitative Composition

Each Metrogyl tablet contains 200 mg or 400 mg of metronidazole.

Metrogyl contains lactose. For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Metrogyl 200 mg tablets: white tablets marked with MZ/200 on one side, G on the reverse.

Metrogyl 400 mg tablets: yellow tablets marked with MZ/400 on one side, G on the reverse.

The score line is not intended for breaking the tablet.

4. Clinical Particulars

4.1 Therapeutic indications

Metronidazole is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

Metronidazole is active against a wide range of pathogenic micro-organisms notably species of Bacteroides, Fusobacteria, Clostridia, Eubacteria, anaerobic cocci and Gardnerella vaginalis.

It is also active against Trichomonas, Entamoeba histolytica, Giardia lamblia and Balantidium coli.

Metronidazole is indicated in adults and children for the following indications:

1. The prevention of postoperative infections due to anaerobic bacteria, particularly species of Bacteroides and anaerobic streptococci.

2. The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated.

3. Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male.

4. Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis).

5. All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers).

6. Giardiasis.
7. Acute ulcerative gingivitis.

8. Anaerobically infected leg ulcers and pressure sores.

9. Acute dental infections due to anaerobic organisms (e.g. acute pericoronitis and acute apical infections).

### 4.2 Dose and method of administration

This product is not able to deliver all approved dose regimens.

**Dose**

**Prophylaxis against anaerobic infection**

Chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.

**Adults**

400 mg at 8-hourly intervals during the 24 hours preceding operation, followed by postoperative intravenous or rectal administration until the patient is able to take tablets.

**Children**

Children less than 12 years: 20 – 30 mg/kg as a single dose given 1 to 2 hours before surgery.

**Treatment of established anaerobic infection**

The duration of a course of Metrogyl treatment is about 7 days but it will depend upon the seriousness of the patient’s condition as assessed clinically and bacteriologically.

**Adults**

800 mg followed by 400 mg 8 hourly.

**Children**

Children from 8 weeks to 12 years of age: the usual dose is 20 – 30 mg/kg as a single dose or divided into 7.5 mg/kg every 8 hours. The daily dose may be increased to 40 mg/kg depending on the severity of the infection. Duration of treatment is usually 7 days.

**Protozoal and other infections**

<table>
<thead>
<tr>
<th>Dosage is given in terms of metronidazole or metronidazole equivalent</th>
<th>Duration of dosage in days</th>
<th>Adults and children over 10 years</th>
<th>Children+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>7 to 10 years</td>
<td>3 to 7 years</td>
</tr>
<tr>
<td><strong>Urogenital trichomoniasis</strong> Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently.</td>
<td>7 or 5 - 7</td>
<td>2000 mg as a single dose or 400 mg twice daily</td>
<td>40 mg/kg orally as a single dose or 15-30 mg/kg/day divided in 2 – 3 doses; not to exceed 2000 mg/dose</td>
</tr>
<tr>
<td><strong>Bacterial vaginosis</strong></td>
<td>5 - 7 or 1</td>
<td>400 mg twice daily</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2000 mg as a single dose</td>
<td>-</td>
</tr>
</tbody>
</table>
Dosage is given in terms of metronidazole or metronidazole equivalent

<table>
<thead>
<tr>
<th>Duration of dosage in days</th>
<th>Adults and children over 10 years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>7 to 10 years</td>
<td>3 to 7 years</td>
</tr>
<tr>
<td><strong>Amoebiasis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Invasive intestinal disease in susceptible subjects.</td>
<td>5</td>
<td>800 mg three times daily</td>
</tr>
<tr>
<td>(b) Intestinal disease in susceptible subjects and chronic amoebic hepatitis</td>
<td>5 – 10</td>
<td>400 mg three times daily</td>
</tr>
<tr>
<td>(c) Amoebic liver abscess, also other forms of extra-intestinal amoebiasis</td>
<td>5</td>
<td>400 mg three times daily</td>
</tr>
<tr>
<td>(d) Symptomless cyst passers</td>
<td>5 – 10</td>
<td>400 – 800 mg three times daily</td>
</tr>
<tr>
<td></td>
<td>Alternatively, doses may be expressed by body weight: 35 to 50 mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400 mg/day</td>
<td></td>
</tr>
<tr>
<td><strong>Giardiasis</strong></td>
<td>3</td>
<td>2000 mg once daily or</td>
</tr>
<tr>
<td>5</td>
<td>400 mg three times daily or</td>
<td>-</td>
</tr>
<tr>
<td>7 – 10</td>
<td>500 mg twice a day</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Alternatively, as expressed in mg per kg of body weight: 15 – 40 mg/kg/day divided in 2 – 3 doses</td>
<td></td>
</tr>
<tr>
<td><strong>Acute ulcerative gingivitis</strong></td>
<td>3</td>
<td>200 mg three times daily</td>
</tr>
<tr>
<td><strong>Acute dental infections</strong></td>
<td>3-7</td>
<td>200 mg three times daily</td>
</tr>
<tr>
<td><strong>Leg ulcers and pressure sores</strong></td>
<td>7</td>
<td>400 mg three times daily</td>
</tr>
</tbody>
</table>

+Children and infants weighing less than 10 kg should receive proportionately smaller dosages.

**Eradication of Helicobacter pylori in paediatric patients**

As part of a combination therapy, 20 mg/kg/day not to exceed 500 mg twice daily for 7 – 14 days. Official guidelines should be consulted before initiating therapy.

**Special populations**

**Elderly**

Metronidazole is well tolerated by the elderly, but a pharmacokinetic study suggests cautious use of high dosage regimens in this age group.

**Method of administration**
Metrogyl tablets should be swallowed with water (not chewed). It is recommended that the tablets be taken during or after a meal.

4.3 Contraindications

Known hypersensitivity to nitroimidazoles, metronidazole or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Regular clinical and laboratory monitoring (especially leucocyte count) are advised if administration of Metrogyl for more than 10 days is considered to be necessary and patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures).

Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system disease due to risk of neurological aggravation.

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 medicine 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 as 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, 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 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 Metrogyl need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IPD) or continuous ambulatory peritoneal dialysis (CAPD).

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. Metrogyl 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.

Patients should be warned that metronidazole may darken urine.
Due to inadequate evidence on the mutagenicity risk in humans the use of metronidazole for longer treatment than usually required should be carefully considered.

Metronidazole has no direct activity against aerobic -or facultative anaerobic bacteria.

4.5 Interaction with other medicines and other forms of interaction

Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. There is no interaction with heparin.

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.

Patients receiving phenobarbital metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours.

Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards, because of the possibility of a disulfiram-like (Antabuse) reaction. Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.

Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when co-administration is necessary.

Metronidazole reduces the clearance of 5-fluorouracil and can therefore result in increased toxicity of 5-fluorouracil.

Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding

There is inadequate evidence of the safety of metronidazole in pregnancy, but it has been in wide use for many years without apparent ill consequence. Nevertheless, Metrogyl, like other medicines, should not be given during pregnancy or during lactation unless the physician considers it essential; in these circumstances the short, high-dose regimens are not recommended.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency of adverse events listed below is defined using the following convention:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).
Serious adverse reactions occur rarely with standard recommended regimens. Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

**Blood and lymphatic system disorders**

Very rare: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia

Not known: leucopenia

**Immune system disorders**

Rare: anaphylaxis

Not known: angioedema, urticaria, fever

**Immune system disorders**

Rare: anaphylaxis

Not known: angioedema, urticaria, fever

**Metabolism and nutrition disorders**

Not known: anorexia

**Psychiatric disorders**

Very rare: psychotic disorders, including confusion and hallucinations

Not known: depressed mood

**Nervous system disorders**

Very rare: encephalopathy (e.g. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug

Very rare: drowsiness, dizziness, convulsions, headaches

Not known: during intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced

Not known: aseptic meningitis

**Eye disorders**

Very rare: vision disorders such as diplopia and myopia, which in most cases is transient

Not known: optic neuropathy/neuritis

**Ear and labyrinth disorders**

Not known: hearing impaired/hearing loss (including sensorineural), tinnitus

**Gastrointestinal disorders**

Not known: taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastrointestinal disturbances such as epigastric pain and diarrhoea

**Hepatobiliary disorders**

Very rare: increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, jaundice and pancreatitis which is reversible on drug withdrawal
Very rare: cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs

**Skin and subcutaneous tissue disorders**

Very rare: skin rashes, pustular eruptions, acute generalised exanthematous pustulosis, pruritus, flushing

Not known: erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption

**Musculoskeletal, connective tissue and bone disorders**

Very rare: myalgia, arthralgia.

**Renal and urinary disorders**

Very rare: darkening of urine (due to metronidazole metabolite)

**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. Healthcare professionals are asked to report any suspected adverse reactions [https://nzphvc.otago.ac.nz/reporting/](https://nzphvc.otago.ac.nz/reporting/).

**4.9 Overdose**

Single oral doses of metronidazole, up to 12 g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation. There is no specific antidote for metronidazole overdosage. In cases of suspected massive overdose, symptomatic and supportive treatment should be instituted.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

**5. Pharmacological Properties**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antibacterials for systemic use, ATC code: J01X D01

Metronidazole has antiprotozoal and antibacterial actions and is effective against *Trichomonas vaginalis* and other protozoa including *Entamoeba histolytica* and *Giardia lamblia* and against anaerobic bacteria.

**5.2 Pharmacokinetic properties**

**Absorption**

Metronidazole is rapidly and almost completely absorbed on administration; peak plasma concentrations occur after 20 minutes to 3 hours.

**Elimination**

The half-life of metronidazole is 8.5 ± 2.9 hours.

Metronidazole can be used in chronic renal failure; it is rapidly removed from the plasma by dialysis.

Metronidazole is excreted in breast milk but the intake of a suckling infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants.
5.3 Preclinical safety data

Metronidazole has been shown to be carcinogenic in the mouse and in the rat following chronic oral administration however similar studies in the hamster have given negative results. Epidemiological studies have provided no clear evidence of an increased carcinogenic risk in humans.

Metronidazole has been shown to be mutagenic in bacteria in vitro. In studies conducted in mammalian cells in vitro as well as in rodent or humans in vivo, there was inadequate evidence of a mutagenic effect of metronidazole, with some studies reporting mutagenic effects, while other studies were negative.

6. Pharmaceutical Particulars

6.1 List of excipients

Metrogyl tablets also contain:

- lactose
- disodium edetate
- ethylcellulose
- sodium starch glycollate
- colloidal anhydrous silica
- guar gum
- magnesium stearate
- quinoline yellow C147005 (400 mg tablets)

Metrogyl tablets are gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

HDPE bottle with PP cap. Pack-size of 250 tablets (200 mg) and 21 tablets (400 mg).

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
9. Date of First Approval

11 July 2019

10. Date of Revision of the Text

9 January 2020

Summary table of changes

<table>
<thead>
<tr>
<th>Section</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Added statement that the score line is not intended for breaking the tablet</td>
</tr>
<tr>
<td>4.2</td>
<td>Removed advice that the 200 mg tablet may be halved</td>
</tr>
<tr>
<td>4.4</td>
<td>Severe skin reaction added to warnings and precautions</td>
</tr>
<tr>
<td>4.8</td>
<td>Acute generalised exanthematous pustulosis added to skin and subcutaneous tissue disorders</td>
</tr>
<tr>
<td>5.1</td>
<td>Antiparasitic and antibacterial actions added</td>
</tr>
</tbody>
</table>