NEW ZEALAND DATA SHEET

METROGYL

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.

Excipients with known effect: Metrogyl tablets contain sulfites, galactose and sugars as 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

Anaerobic Infections

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.

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

7.5 mg/kg 8-hourly.

Elderly

Caution is advised in the elderly, particularly at high doses, although there is limited information available of modification of dosage.

Treatment of established anaerobic infection

Adults

800 mg followed by 400 mg 8-hourly.

Children

7.5 mg/kg every 8-hourly.

Treatment of Protozoal and other infections

See table below

Table 1 – Treatment of protozoal and other infections

Infections	Duration of dosage in days	Adults and children over 10 years**	Children+		
			7 to 10 years	**3 to 7 years**	**1 to 3 years**
Urogenital trichomoniasis *Where re-infection is likely, the consort should receive a similar course of treatment concurrently***.**	7	200 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
	2	800 mg in the am and 1200 mg in the pm	-	-	-
	1	2.0 g as a single dose	-	-	-
Non-specific vaginosis	7	400 mg twice daily	-	-	-
	1	2.0 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
(b) Intestinal disease in susceptible subjects and chronic amoebic hepatitis	5 – 10	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
(c) Symptomless cyst passers	5 – 10	400 – 800 mg three times daily	200 – 400 mg three times daily	100 – 200 mg four times daily	100 – 200 mg three times daily
Giardiasis	3	2.0 g once daily	1.0 g once daily	600 – 800 mg once daily	500 mg once 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 dental infections	3-7	200 mg three times daily	-	-	-
Leg ulcers and pressure sores	7	400 mg three times daily	-	-	-

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

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

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

- Patients with evidence of or a history of blood dyscrasias should not receive the drug since upon occasion a mild leucopenia has been observed during administration. However, no persistent haematological abnormalities have been observed in animals or clinical studies.
- Active organic disease of the central nervous system.
- Known hypersensitivity to metronidazole, other imidiazoles or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Alcohol

Alcoholic beverages and drugs containing alcohol, should not be consumed by patients being treated with metronidazole and for at least a day after treatment as nausea, vomiting, abdominal cramps, headaches, tachycardia and flushing may occur. There is the possibility of a disulfiram-like (Antabuse) effect reaction.

Long term therapy

Regular clinical and laboratory monitoring (haematological tests especially leucocyte count) are advised if administration of Metrogyl for longer than the usually recommended duration is considered to be necessary and patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, vertigo, convulsive seizures). If leucopenia or abnormal neurological signs occur, the drug should be discontinued immediately.

Surgical drainage

Use of metronidazole does not obviate the need for aspirations of pus whenever indicated.

Impaired renal function

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 removed during an eight-hour period of dialysis. Metronidazole should therefore be 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).

Patients should be warned that metronidazole may darken urine (due to metronidazole metabolite).

Impaired hepatic function

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 impaired liver function or hepatic encephalopathy. The daily dosage should be reduced to one-third and may be administered once daily. Metronidazole may interfere with certain chemical analyses of serum aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), triglycerides and hexokinase glucose to give abnormally low values.

Nervous system

Caution is advised in patients with active disease of the central nervous system other than brain abscess. 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. Treatment should be immediately discontinued if signs of neuropathy or encephalopathy are noticed.

Suicidal ideation

Cases of suicidal ideation with or without depression have been reported during treatment with metronidazole. Patients should be advised to discontinue treatment and contact their healthcare provider immediately if they experience psychiatric symptoms during treatment.

Infections

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

Candida overgrowth in the gastrointestinal or genital tract may occur during metronidazole therapy and require treatment with a candidacidal drug.

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 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.

Severe bullous skin reactions

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 (see section 4.8). If symptoms or signs of SJS, TEN or AGEP are present, metronidazole treatment must be immediately discontinued.

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

Effects on laboratory tests

Metronidazole 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.

4.5 Interaction with other medicines and other forms of interaction

Some potentiation of anticoagulant effect (and increased haemorrhagic risk caused by decreased hepatic catabolism) 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 more frequently monitored. No interactions have been reported with anticoagulants of the heparin type. However, anticoagulant activity should be routinely monitored with these products.

Plasma levels of lithium may be increased by 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.

Patients receiving phenobarbitone or phenytoin 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 one day 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. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.

Metronidazole should be used with caution in patients receiving carmustine and/or cyclophosphamide.

Concomitant use of ciclosporin and metronidazole could result in increased serum levels of ciclosporin. When it is necessary to co-administer the two together close monitoring of serum ciclosporin and creatinine is advisable.

The clearance of 5-fluorouracil is reduced resulting in increased toxicity of 5-fluorouracil.

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

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

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B2

There is inadequate evidence of the safety of metronidazole in pregnancy, However, as Metrogyl crosses the placental barrier it,, 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.

Breast-feeding

As metronidazole is excreted in human milk, unnecessary exposure to the drug should be avoided.

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, vertigo, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Serious adverse reactions occur very rarely with standard recommended regimens.

Gastrointestinal disorders

When given orally, metronidazole is well tolerated. The most common adverse reactions refer to the gastrointestinal tract, particularly nausea, sometimes accompanied by headache, anorexia and occasionally vomiting, diarrhoea, epigastric pain or distress and abdominal cramping; constipation, taste disorders and oral mucositis have also been reported. A metallic, sharp, unpleasant taste is not unusual. Cases of pancreatitis which abated on withdrawal of the drug, have been reported. Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing or headache. A modification of the taste of alcoholic beverages has also been reported.

Furry tongue, tongue discolouration, glossitis and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during effective therapy.

Body as a whole

Hypersensitivity reactions include urticaria, fever, rash, pruritus, flushing, angioedema and anaphylactic shock. Nasal congestion and dryness of the mouth have been reported. Mild erythematous eruptions have been experienced, as have fleeting joint pains sometimes resembling serum sickness. Pustular eruptions and acute generalised exanthematous pustulosis have been reported. Fixed drug eruption has been reported. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported.

Peripheral and Central Nervous System

Drowsiness, dizziness, headache and uncoordinated movements have been reported. During intensive and/or prolonged metronidazole therapy, a few instances of peripheral neuropathy (characterised mainly by numbness or paraesthesia of an extremity) or convulsions have been reported. There have been reports of encephalopathy (e.g. confusion, vertigo) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor). In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of metronidazole, such subjects should be specifically warned about these reports and should be told to stop the drug and report immediately if any neurological symptoms occur. Aseptic meningitis has been reported.

Psychiatric Disorders

Psychotic disorders, such as confusion and hallucinations have been reported. Depression, depressed mood, insomnia, irritability and weakness have also been reported.

Frequency not known: vertigo

Eye disorders

Optic neuropathy/neuritis and transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity and changes in colour vision have been reported.

Ear and Labyrinth Disorders

Impaired hearing/hearing loss (including sensorineural) and tinnitus have been reported.

Blood and lymphatic system disorders

Cases of agranulocytosis, neutropenia and thrombocytopenia have been reported. A moderate leucopenia has been reported in some patients. If this occurs, the total leucocyte count may be expected to return to normal after the course of medication is completed. One case of bone marrow

depression has been reported. If profound bone marrow suppression occurs, use of metronidazole should be ceased and appropriate supportive therapy instituted.

Hepatobiliary disorders

Increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice, have been reported.

Cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Genito-urinary Tract

Proliferation of *Candida* also may occur in the vagina. Dryness of the vagina or vulva, pruritus, dysuria, cystitis and a sense of pelvic pressure have been reported. Very rarely dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis and pyuria have occurred in patients receiving the drug.

Instances of darkened urine have been reported and this manifestation has been the subject of special investigation. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole. It seems certain that it is of no clinical significance and may be encountered only when metronidazole is administered in higher than recommended doses.

Cardiovascular

Flattening of the T wave may be seen in ECG tracings.

Frequency not known: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

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/.

4.9 Overdose

Symptoms of overdosage are limited to vomiting, ataxia and slight disorientation. Uneventful recovery has followed attempts at suicide and accidental overdoses with quantities of 30 and 60 x 200 mg tablets, and single oral doses of metronidazole, up to 12 g. There is no specific treatment for gross overdosage of metronidazole. Treatment should be symptomatic and supportive.

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

Microbiology

Metronidazole has antiprotozoal and anaerobic antibacterial actions and is effective against a wide range of pathogenic micro-organisims 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*.

It is suggested that unchanged metronidazole penetrates the protozoan cell, where the nitro group is reduced to a hydroxyl or amine group which reacts with DNA and stops nucleic acid synthesis.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Metronidazole is widely distributed into most body tissues and fluids where it achieves concentrations similar to those in plasma. Metronidazole is not protein bound to any significant degree. Metronidazole is metabolised by oxidation in the liver to a number of metabolites, one of which (the hydroxy metabolite) has some antibacterial activity.

Elimination

The elimination half-life of metronidazole is 7-8 hours, and that of the hydroxyl metabolite slightly longer. About 55 to 80 percent of an administered dose is excreted in the urine as nitro-containing compounds, of which unchanged metronidazole and the hydroxymethyl homologue each comprise about one third. The fate of the remainder is unknown.

Metronidazole should be administered with caution to patients with advanced hepatic insufficiency.

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

Carcinogenicity/Mutagenicity

Metronidazole has been shown to be carcinogenic in the mouse and in the rat. However similar studies in the hamster have given negative results and extensive human epidemiological studies have provided no evidence of 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.

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)

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

Arrotex Pharmaceuticals (NZ) Limited:
C/o Quigg Partners
Level 7, The Bayleys Building
36 Brandon Street,
Wellington 6011, New Zealand
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9. Date of First Approval

11 July 2019

10. Date of Revision of the Text

7 October 2024

Summary table of changes

Section	Summary of new information
8	Update to sponsor's details