NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Flagyl 500 mg suppositories

Flagyl-S 200 mg/5 mL oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flagyl suppositories contain 500 mg metronidazole.

Flagyl-S suspension contains 320 mg metronidazole benzoate, equivalent to 200 mg metronidazole, in each 5 mL.

Flagyl-S suspension also contains 3.01 g sucrose, 4.00 mg methyl parahydroxybenzoate, 1.00 mg propyl parahydroxybenzoate and 0.04 mL ethanol, in each 5 mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository and oral suspension.

Flagyl suppositories are creamy in colour, smooth faced and torpedo shaped.

Flagyl-S is a white to cream-yellow (buff) coloured suspension easily dispersible with gentle shaking.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

1. The prevention of post-operative 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

Flagyl suppositories are unsuitable for initiating treatment of serious conditions owing to slower absorption and lower plasma concentrations of metronidazole.

Flagyl suspension should be taken at least one hour before a meal.

Anaerobic Infections

The duration of a course of Flagyl 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.

Oral:

Adults: 400 mg at 8-hourly intervals during the 24 hours preceding operation, followed by post-operative intravenous or rectal administration until the patient is able to take oral medication.

Children: 7.5 mg/kg 8-hourly.

Rectal:

Adults: 1 g 8-hourly.

Children: One half or a quarter of a 500 mg suppository 8 hourly.

Elderly:

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

Treatment of established anaerobic infection

Oral dosage is given in terms of metronidazole or metronidazole equivalent.

Oral:

Adults: 800 mg followed by 400 mg 8-hourly.

Children: 7.5 mg/kg 8-hourly.

Rectal:

Adults: 1g 8-hourly. Substitute oral medication as early as possible. If rectal administration is prolonged beyond 3 days, reduce dose to 1g 12-hourly for remainder of course.

Treatment of Protozoal and other Infections

See table below:

Table 1 - Treatment of Protozoal and Other Infections

Infection	Duration of dosage in days	Adults and children over 10 years‡	Children† - 7 to 10 years	Children† - 3 to 7 years	Children † - 1 to 3 years
Urogenital trichomoniasis (where re-infection is likely, the consort should receive a similar course of treatment concurrently)	7	200 mg 3 x daily	100 mg 3 x daily	100 mg twice daily	50 mg 3 x daily
	2	800 mg in the am. and 1200 mg in the pm.	-	-	-
	1	2.0 g as a single dose	-	-	-
Non-specific vaginitis	7	400 mg twice daily	-	-	-
	1	2.0 g as a single dose	-	-	-
Amoebiasis			-	-	-
(a) Invasive intestinal disease in susceptible subjects	5	800 mg 3 x daily	400 mg 3 x daily	200 mg 4 x daily	200 mg 3 x daily
(b) Intestinal disease in susceptible subjects and chronic amoebic hepatitis	5-10	400 mg 3 x daily	200 mg 3 x daily	100 mg 4 x daily	100 mg 3 x daily
(c) Symptomless cyst passers	5-10	400-800 mg 3 x daily	200-400 mg 3 x daily	100-200 mg 4 x daily	100-200 mg 3 x daily
Giardiasis	3	2.0 g once daily	1.0 g once daily	600-800 mg once daily	500 mg once daily

Infection	Duration of dosage in days	Adults and children over 10 years‡	Children† - 7 to 10 years	Children† - 3 to 7 years	Children † - 1 to 3 years
Acute ulcerative gingivitis	3	200 mg 3 x daily	100 mg 3 x daily	100 mg 2 x daily	50 mg 3 x daily
Acute dental infections	3 - 7	200 mg 3 x daily	-	-	-
Leg ulcers & pressure sores	7	400 mg 3 x daily	-	-	-
Anaerobic infections (general)	See Data Sheet Text				

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

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

4.3 CONTRAINDICATIONS

1. 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 its administration. However, no persistent haematological abnormalities have been observed in animals or clinical studies.
2. Active organic disease of the central nervous system.
3. Hypersensitivity to metronidazole and other imidazoles.
4. Patients with Cockayne Syndrome. Severe irreversible hepatoxicity/acute liver failure with fatal outcomes have been reported after initiation of metronidazole in patients with Cockayne Syndrome (see Section 4.8 Adverse effects (undesirable effects)).

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

If, for compelling reasons, metronidazole must be administered for longer than the usually recommended duration it is recommended that haematological tests, especially leucocyte count, should be carried out regularly, and that patients should be monitored for adverse reactions such as peripheral or central neuropathy (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 aspiration 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 Flagyl 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. Flagyl 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 a day. 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 diseases due to the 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.

Use of condoms and diaphragms

The simultaneous use of Flagyl suppositories with condoms or diaphragms may increase the risk of rupture of the latex.

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.

Posterior Reversible Encephalopathy Syndrome (PRES)

Patients treated with metronidazole have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking metronidazole present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure control and immediate discontinuation of metronidazole is advised. Most patients completely recover after appropriate measures are taken.

Severe bullous skin reactions

Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP) and Drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with metronidazole (see section 4.8). If symptoms or signs of SJS, TEN, AGEP or DRESS are present, metronidazole treatment must be immediately discontinued.

Inflammatory bowel disease (IBD)

Use of metronidazole may increase the risk of subsequent inflammatory bowel disease (IBD).

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 cyclosporin and metronidazole could result in increased serum levels of cyclosporin. When it is necessary to co-administer the two together close monitoring of serum cyclosporin 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 Flagyl 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-dosage regimes 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 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. Drug reactions with eosinophilia and systemic symptoms (DRESS) have 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, posterior reversible encephalopathy syndrome (PRES)

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.

Cases of severe irreversible hepatoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (latency from drug start to signs of liver failure as short as 2 days) (see Section 4.3 Contraindications).

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://pophealth.my.site.com/carmreportnz/s/

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 Flagyl. Treatment should be symptomatic and supportive.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, ATC code J01X D01.

Microbiology

Antiprotozoal agent; anaerobic antibacterial agent.

Flagyl 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*.

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

The bioavailability of metronidazole in Flagyl suppositories is 60-80%. Effective blood concentrations are achieved 5-12 hours after the first suppository and are maintained by the recommended 8-hourly regimen.

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

Flagyl suppositories contain hard fat as the excipient.

Flagyl-S oral solution contains the following excipients:

- sucrose
- ethanol
- monobasic sodium phosphate dihydrate
- aluminium magnesium silicate
- methyl hydroxybenzoate
- propyl hydroxybenzoate
- terpeneless orange oil
- citrus limon
- purified water

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

3 years

Dilution of Flagyl-S suspension, if necessary, should be carried out with syrup B.P. The diluted suspension has a shelf life of 14 days.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Suppositories

Pack size: blister pack 10 suppositories.

Suspension

Pack size: 100 mL glass bottle.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644
Freecall: 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

Flagyl suppositories: 25 August 1977

Flagyl-S oral suspension: 22 December 1980

10 DATE OF REVISION OF THE TEXT

18 June 2025

Summary table of changes

Section	Change
4.4	Addition of DRESS to severe bullous skin reactions
4.8	Addition of DRESS as a reported adverse effect for Body as a whole