AUSTRALIAN PRODUCT INFORMATION – FLAGYL S (metronidazole benzoate) ORAL SUSPENSION

1 NAME OF THE MEDICINE

Metronidazole benzoate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flagyl S suspension 6.4% w/v (metronidazole 200 mg/5 mL) contains 320mg of metronidazole benzoate, equivalent to 200mg of metronidazole, per 5mL.

Metronidazole benzoate is 1-(2-benzoyloxyethyl)-2-methyl-5-nitroimidazole.

List of excipients with known effect: hydroxybenzoates, sugars.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

A white or cream suspension with a slight yellow tinge, and with an odour of orange and lemon.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Anaerobic Infections

Treatment of infections in which anaerobic bacteria have been identified or are suspected as pathogens, particularly *Bacteroides fragilis* and other species of bacteroides, and other species such as fusobacteria, eubacteria, clostridia and anaerobic streptococci. Flagyl has been used successfully in septicaemia; bacteraemia; brain abscess; necrotising pneumonia; osteomyelitis; puerperal sepsis; pelvic abscess; pelvic cellulitis; postoperative wound infections.

Notes:
a) Because of the slow absorption and delayed peak plasma level, Flagyl S suspension is not recommended for use in the acute situation.

b) Metronidazole is inactive against aerobic and facultative anaerobic bacteria.

Other Indications

Oral treatment of urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male, and for the treatment of bacterial vaginosis. The male consort of females suffering from urogenital trichomoniasis should be treated concurrently; all forms of amoebiasis (intestinal

and extraintestinal disease and that of symptomless cyst passers); giardiasis; acute ulcerative gingivitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Flagyl S suspension is administered orally.

It is recommended that the dose should be taken at least one hour before a meal.

Rinse out the measuring glass to ensure that the correct dose is taken.

A maximum of 2.4 g should not be exceeded during a 24 hour period. Dosages should be decreased in patients with severe hepatic disease; plasma metronidazole levels should be monitored.

In elderly patients the pharmacokinetics of metronidazole may be altered and therefore monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

Oral

(Summarised in Table 1)

Table 1 - Flagyl

ORAL DOSAGE					
Infection	Duration of dosage in days	Adults and children over 12 years	Children 7-12 years	Children 3-7 years	Children 1-3 years
Anaerobic Infections (treatment)	7	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
Urogenital trichomoniasis	7 or	200 mg three times daily	100 mg three times daily	100 mg two times daily	50 mg three times daily
To prevent reinfection the consort should receive a similar course or treatment concurrently.	1	2 g			
If treated during the 2nd or 3rd trimester, the one day course of therapy should not be used as it results in higher serum levels which reach the foetal circulation. (see PRECAUTIONS, Use in Pregnancy)		When repeat courses of the drug are required, it is recommended that an interval of 4 to 6 weeks elapse between courses and the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leucocyte counts should be made before and after re-treatment			
Bacterial vaginosis	1 or	2 g daily	-	-	-
	7	400 mg three times daily	-	-	-
Amboebiasis 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 less 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

ORAL DOSAGE					
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	100 mg three times daily
d) Symptomless cyst passers. The upper range of dosages and duration of treatment seem to be necessary in temperate climate countries.	5-10	400 mg to 800 mg three times daily	200 mg to 400 mg three times daily	100 mg to 200 mg four times daily	100 mg to 200 mg three times daily
Giardiasis	3	2 g daily	1 g once daily	600 mg once daily	400 mg once daily
Acute ulcerative gingivitis	3	200 mg three times daily	100 mg three times daily	100 mg two times daily	50 mg three times daily

Surgical Prophylaxis

Note: Prevention of infections at the surgical site requires that adequate tissue concentration of the drug should have been achieved at the time of surgery. The dose and route of administration should be selected in each case to achieve this objective.

As oral ingestion is often prohibited 12 hours or longer before surgery, and may not be practical for a variable period following surgery, the suspension is not considered to be an appropriate formulation for prophylactic use. In addition, due to the lower and delayed peak serum levels with this formulation each dose should be the equivalent of 800 mg of metronidazole. The first dose should be administered three to four hours before surgery, then repeated every eight hours for 24 hours.

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 its administration. However, no persistent haematological abnormalities have been observed in animals or clinical studies.

Active organic disease of the central nervous system.

Hypersensitivity to metronidazole and other imidazoles.

Patients with Cockayne Syndrome. Severe irreversible hepatotoxicity/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 as nausea, vomiting, abdominal cramps, headaches, tachycardia and flushing may occur.

Candidiasis

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) or acute generalised exanthematous pustulosis (AGEP) have been reported with metronidazole (see Section 4.8 Adverse effects (undesirable effects)). If symptoms or signs of SJS, TEN or AGEP are present, metronidazole treatment must be immediately discontinued.

Long term therapy

If metronidazole is to be administered for more than 10 days, it is recommended that haematological tests, especially total and differential leucocyte counts, be carried out regularly and that patients be monitored for adverse reactions such as peripheral or central neuropathy (such as paresthesia, ataxia, dizziness, vertigo, convulsive seizures). If leucopenia or abnormal neurological signs occur, the drug should be discontinued immediately.

Inflammatory bowel disease (IBD)

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

Surgical drainage

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

Nervous system

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 damage.

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

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 in renal impairment

In patients on twice weekly haemodialysis, metronidazole and its major active metabolite are rapidly removed during an 8 hour period of dialysis, so that the plasma concentration quickly falls below the therapeutic range. Hence, a further dose of metronidazole would be needed after dialysis to restore an adequate plasma concentration. In patients with renal failure the half-life of metronidazole is unchanged, but those of its major metabolites are prolonged 4-fold or greater. The accumulation of the hydroxy metabolite could be associated with side effects and measurement of its plasma concentration by high pressure liquid chromatography (HPLC) has been recommended.

Use in hepatic impairment

No information available. As metronidazole is partly metabolised in the liver, caution should be exercised in patients with impaired liver function or hepatic encephalopathy.

Flagyl may interfere with certain chemical analysis of serum aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), triglycerides and glucose hexokinase to give abnormally low values.

Use in the elderly

See Section 4.2 Dose and method of administration.

Paediatric use

See Section 4.2 Dose and method of administration.

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Metronidazole enhances the activity of warfarin, and if metronidazole is to be given to patients receiving this or other anticoagulants, the dosages of the latter should be recalibrated. There is an increased haemorrhagic risk caused by decreased metabolism. Prothrombin times should be monitored as should anticoagulant activity.

The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital (phenobarbitone), may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

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.

In patients stabilised on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity.

Serum lithium and serum creatinine levels and electrolytes should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

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.

Carmustine, cyclophosphamide monohydrate: Metronidazole should be used with caution in patients receiving these drugs.

There is a risk of ciclosporin serum levels increasing when it is used in combination with metronidazole. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Metronidazole used in combination with 5-fluorouracil may lead to reduced clearance of 5-fluorouracil, resulting in increased toxicity.

Patients should be advised not to take alcohol during therapy or for at least one day afterwards because of the possibility of a disulfiram-like (antabuse) effect reaction.

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

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

Effects on fertility

No data available.

Use in pregnancy

Category B2

Metronidazole should not be given in the first trimester of pregnancy as it crosses the placenta and enters foetal circulation rapidly. As its effects on foetal organogenesis are not known, its use in pregnancy should be carefully evaluated. Although it has not been shown to be teratogenic in either human or animal studies, such a possibility cannot be excluded.

Use of metronidazole for trichomoniasis in the second and third trimesters should be restricted to those in whom local palliative treatment has been inadequate to control symptoms.

Use in lactation

Metronidazole is secreted in breast milk (see Section 5.2 Pharmacokinetic properties). In view of its tumorigenic and mutagenic potential (see Section 5.3 Preclinical safety data), breastfeeding is not recommended.

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. See Section 4.4 Special warnings and precautions for use and see Section 4.8 Adverse effects (Undesirable effects).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Gastrointestinal effects

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, oral mucositis and taste disorders 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 rash, pruritus, flushing, urticaria, fever, 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.

Liver

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; all spiramycin except one case of tetracycline.

Cases of severe irreversible hepatotoxicity/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).

Haematology

A moderate leucopenia may be observed occasionally. 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 Flagyl should be ceased and appropriate supportive therapy instituted. Cases of agranulocytosis, neutropenia or thrombocytopenia have been reported.

Psychiatric/CNS disorders

Dizziness, vertigo, incoordination, headache and convulsive seizures have been reported. Psychotic disorders such as confusion and hallucinations have been reported. Depression, depressed mood, insomnia, irritability, weakness have been experienced, as has peripheral neuropathy, characterised mainly by numbness or paraesthesia of an extremity. There have been reports of encephalopathy (e.g. confusion, vertigo) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor), which may resolve with discontinuation of the drug. 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.

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.

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 suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 OVERDOSE

Symptoms

Overdosage with metronidazole appears to be associated with very few abnormal signs or symptoms. Disorientation, ataxia and vomiting may occur, especially after ingestion of large amounts. In case of suspected massive overdosages, a symptomatic and supportive treatment should be instituted.

Single oral doses of metronidazole, up to 12 g, have been reported in suicide attempts and accidental overdoses.

Treatment

There is no specific antidote for metronidazole overdosage. In cases of suspected overdosage, a symptomatic and supportive treatment should be instituted.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

Metronidazole benzoate itself is not systemically available following oral administration. It is hydrolysed before or during absorption through the gut wall so that only metronidazole can be detected in the circulation.

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

Metronidazole is effective *in vitro* against several species of anaerobic bacteria, particularly *Bacteroides fragilis* and other species of bacteroides, and other species such as fusobacteria, eubacteria, clostridia, and anaerobic streptococci. The MIC for most susceptible anaerobes is < 6.2 micrograms/mL.

Note: Metronidazole is inactive against aerobic and facultative anaerobic bacteria.

Metronidazole is active against a wide range of pathogenic microorganisms notably Trichomonas vaginalis and other trichomonads, *Entamoeba histolytica*, *Giardia lamblia*, *Balantidium coli* and the causative organisms of acute ulcerative gingivitis.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Maximum mean plasma metronidazole concentration are 16.6 micrograms/mL at 5.1 hours after administration of a single oral dose of metronidazole benzoate, equivalent to 2 g metronidazole and 4.6 micrograms/mL at 3.2 hours after administration of a single oral dose of metronidazole benzoate, equivalent to 400 mg metronidazole. An oral dose of two 200 mg tablets of metronidazole in the same trial gave mean peak serum levels of 8.5 microgram/mL at 0.8 hours after administration. Total absorption from metronidazole benzoate suspension was somewhat lower than from the tablets. In children the time to reach peak serum level is quite variable (3.6 to 5.1 hours).

Mean elimination half-lives are 9.7 hours following metronidazole benzoate suspension (2 g metronidazole) and 8.6 hours following metronidazole benzoate suspension (400 mg metronidazole).

Distribution

Metronidazole is widely distributed in body tissues and fluids and is not protein bound to any significant degree.

Metronidazole diffuses across the blood-brain barrier and placenta and is found in the breast milk of nursing mothers in concentrations equivalent to those in serum.

Metabolism

No data available.

Excretion

Most of the dose is excreted in the urine as metronidazole and its metabolites including oxidation products and glucuronides.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In studies on the mutagenic potential of metronidazole, the Ames test was positive while several nonbacterial tests in animals were negative. In the patients with Crohn's disease, metronidazole increased the chromosome abnormalities in circulating lymphocytes. The use of metronidazole for longer treatment than usually required should be carefully weighed (see Section 4.4 Special warnings and precautions for use) and the benefit/risks should, therefore, be carefully assessed in each case particularly in relation to the severity of the disease and the age of the patient.

Carcinogenicity

Metronidazole been shown to be tumorigenic and carcinogenic in rodents.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

aluminium magnesium silicate

ethanol

methyl hydroxybenzoate

monobasic sodium phosphate

natural soluble lemon flavour 50 06-0404 (PI 225)

orange oil terpeneless

propyl hydroxybenzoate

sucrose

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Glass bottle

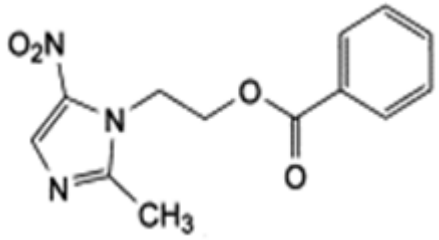
Pack size: 100 mL.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

13182-89-3

Slightly yellow crystalline powder with a melting point of 99 to 102°C. Solubility at 25°C (g/100 mL solvent): 12.2 x 10-3 in water, 2 in ethanol, 5 in methanol and 25.6 in acetone. The pH of metronidazole benzoate suspensions in water is 5 to 6.5.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4. Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

21 October 1991.

10 DATE OF REVISION

25 February 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3	Addition of Cockayne Syndrome
4.4	Deletion of Cockayne Syndrome
4.8	Addition of cases of severe irreversible hepatotoxicity/acute liver failure