

# Data Sheet

## Flagyl and Flagyl-S

### Name of the Medicine

Flagyl metronidazole B.P. 200 mg tablet

Flagyl metronidazole B.P. 400 mg tablet

Flagyl metronidazole B.P. 500 mg suppositories

Flagyl metronidazole 1 g suppositories

Flagyl-S metronidazole benzoate oral suspension equivalent of 200 mg metronidazole/5 mL

### Presentation

Flagyl 200 mg tablets contain 200 mg metronidazole. The 200 mg tablets are circular and biconvex with a diameter of 10.1 mm, off white to cream, film coated, and engraved 'Flagyl 200' around the outer margin.

Flagyl 400 mg tablets contain 400 mg metronidazole. The 400 mg tablets are capsule-shaped, 18.0 mm in length, off-white to cream, film coated, and engraved 'Flagyl 400' on one side.

Flagyl suppositories are creamy coloured and contain 500 mg metronidazole.

Flagyl-S suspension is buff-coloured, each 5 mL containing 320 mg metronidazole benzoate, equivalent to 200 mg metronidazole. Flagyl-S suspension contains 68% w/v sugars, ethanol, methyl and propyl hydroxy-benzoate.

### Uses

#### Actions

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.

#### Pharmacokinetics

##### Absorption

Flagyl tablets are rapidly and almost completely absorbed leading to peak serum levels after 20 minutes to 3 hours. 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.

## **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 (eg. acute pericoronitis and acute apical infections).

## **Dosage and Administration**

Flagyl tablets should be swallowed with water (not chewed). It is recommended that the tablets be taken during or after a meal.

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 tablets.

Children: 7.5 mg/kg 8-hourly.

*Rectal:*

Adults: 1g 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

	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
<b>Urogenital trichomoniasis (where re-infection is likely, the consort should receive a similar course of treatment concurrently)</b>	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	-	-	-
<b>Non-specific vaginitis</b>	7	400 mg twice daily	-	-	-
	1	2.0 g as a single dose	-	-	-
<b>Amoebiasis</b>					
<b>(a) Invasive intestinal disease in susceptible subjects</b>	5	800 mg 3 x daily	400 mg 3 x daily	200 mg 4 x daily	200 mg 3 x daily

	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
<b>(b) Intestinal disease in susceptible subjects and chronic amoebic hepatitis</b>	5-10	400 mg 3 x daily	200 mg 3 x daily	100 mg 4 x daily	100 mg 3 x daily
<b>(c) Symptomless cyst passers</b>	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
<b>Giardiasis</b>	3	2.0 g once daily	1.0 g once daily	600-800 mg once daily	500 mg once daily
<b>Acute ulcerative gingivitis</b>	3	200 mg 3 x daily	100 mg 3 x daily	100 mg 2 x daily	50 mg 3 x daily
<b>Acute dental infections</b>	3 - 7	200 mg 3 x daily	-	-	-
<b>Leg ulcers &amp; pressure sores</b>	7	400 mg 3 x daily	-	-	-
<b>Anaerobic infections (general)</b>	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.

### Contraindications

Known hypersensitivity to metronidazole. Known hypersensitivity to imidazoles.

### Warnings and Precautions

1. 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, convulsive seizures).
2. Treatment should be immediately discontinued if signs of neuropathy or encephalopathy are noticed.
3. There is a possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection might persist.
4. Patients should be warned that metronidazole may darken urine (due to metronidazole metabolite).
5. 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

6. 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 hepatic encephalopathy. The daily dosage should be reduced to one-third and may be administered once a day.
7. 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.
8. 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 effect) reaction.
9. The simultaneous use of Flagyl suppositories with condoms or diaphragms may increase the risk of rupture of the latex.

### **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.

### **Lactation**

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

### **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.

### **Effects on Ability to Drive and Use Machines**

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

### **Adverse Effects**

Serious adverse reactions occur very rarely with standard recommended regimens.

## **Gastrointestinal**

Unpleasant taste in the mouth, metallic taste, furred tongue, nausea, vomiting, diarrhoea, epigastric pain, anorexia, and exceptional and reversible cases of pancreatitis have been reported.

## **Hypersensitivity Reactions**

Urticaria, fever, rash, pruritus, flushing, and angioedema occur occasionally. Anaphylaxis may occur rarely. Very rare pustular eruptions have been reported.

## **Peripheral and Central Nervous System**

Drowsiness, dizziness, headache, uncoordinated movements. During intensive and/or prolonged metronidazole therapy, a few instances of peripheral neuropathy or transient epileptiform seizures have been reported. There have been very rare reports of encephalopathy (e.g. confusion) 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. Transient vision disorders such as diplopia and myopia have been reported.

## **Psychiatric Disorders**

Psychotic disorders, such as confusion and hallucinations have been reported. Depressed mood has been reported.

## **Haematology**

Very rare cases of agranulocytosis, neutropenia and thrombocytopenia have been reported. A moderate leucopenia has been reported in some patients but the white cell count has always returned to normal before or after treatment has been completed.

## **Liver**

Very rare cases of reversible abnormal liver function tests and cholestatic hepatitis, sometimes with jaundice, have been reported.

## **Interactions**

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.

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.

## **Overdosage**

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.

## **Pharmaceutical Precautions**

### **Shelf Life**

Flagyl-S suspension contains 60% w/v sugars. 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.

### **Storage Conditions**

Flagyl tablets	Store below 25°C. Protect from light
Flagyl suppositories	Store below 25°C. Protect from light.
Flagyl-S suspension	Store below 25°C. Protect from light.

## **Medicine Classification**

Prescription Medicine

## **Package Quantities**

Flagyl 200 mg tablets	Containers of 21 x 200 mg tablets.
Flagyl 400 mg tablets	Containers of 100 x 400 mg tablets.
Flagyl 500 mg suppositories	Containers of 10 x 500 mg suppositories
Flagyl 1 g suppositories	Containers of 10 x 1.0 g suppositories.
Flagyl-S suspension	Bottles of 100 mL suspension.

## **Further Information**

Flagyl tablets (200 and 400 mg) contain calcium hydrogen phosphate, starch maize, povidone K30 and magnesium stearate.

Flagyl suppositories contain hard fat.

Flagyl-S suspension contains sodium dihydrogen phosphate, methyl hydroxybenzoate, propyl hydroxybenzoate, ethanol, and liquid sugar.

**Name and Address**

sanofi-aventis new zealand limited  
Level 8, James and Wells Tower  
56 Cawley Street  
Ellerslie, Auckland

**Date of Preparation**

14 October 2009