

PRODUCT INFORMATION

FLAGYL®

NAME OF THE MEDICINE

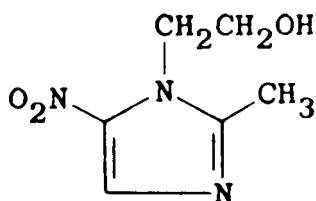
Flagyl Tablets

Flagyl Suppositories

NON-PROPRIETARY NAME

Metronidazole.

CHEMICAL STRUCTURE



CAS NUMBER

Chemical abstracts No: [443-48-1]

DESCRIPTION

Metronidazole is a 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole. It appears as white to brownish cream crystals with melting point of 159 to 162°C. Metronidazole in a saturated aqueous solution has a pH of between 6 and 7.5. Solubility at 20°C (g/100 mL): 1 in water; 0.5 in ethanol; 0.4 in chloroform; slightly soluble in ether, soluble in dilute acids.

The tablet excipients for both strengths are maize starch, calcium hydrogen phosphate, povidone, magnesium stearate, hypromellose, macrogol 400 and purified talc (400 mg tablets only).

The suppository excipient is hard fat.

PHARMACOLOGY

Specific bactericidal activity against important obligate anaerobes.

PHARMACOKINETICS

Maximum concentrations occur in the serum 1 to 2 hours after oral administration and at the end of the infusion after intravenous administration. Traces are detected after 24 hours. The biological half-life of oral and intravenous metronidazole has been determined as 6 to 7 and 7.3 hours respectively.

When administered in suppository form, metronidazole is absorbed slowly and less completely than the oral tablets. Peak serum levels are achieved in approximately 8 hours. After 500 mg and 1 g suppositories the peak serum levels averaged 5.1 microgram/mL and 7.4 micrograms mL, respectively, while the mean total absorption was 82% and 67%, respectively. Its elimination half-life was similar to the intravenous infusion, viz approximately 7.3 hours.

Metronidazole is widely distributed in body tissues and fluids. It 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.

It is not protein bound to any significant degree. Most of the dose is excreted in the urine as metronidazole and its metabolites, including acid oxidation products and glucuronides.

MICROBIOLOGY

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.

INDICATIONS

ANAEROBIC INFECTIONS

ORAL

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.

SUPPOSITORIES

Treatment of anaerobic infection in patients for whom oral medication is not possible or is contraindicated. Prevention of anaerobic infection in high risk situations in patients for whom oral medication is not possible or is contraindicated.

Metronidazole may be used prophylactically to prevent infection of the surgical site which may have been contaminated or potentially contaminated with anaerobic organisms. Procedures in which this may be assumed to have happened include appendectomy, colonic surgery, vaginal hysterectomy, abdominal surgery in the presence of anaerobes in the peritoneal cavity and surgery performed in the presence of anaerobic septicaemia.

Note: 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.

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.

PRECAUTIONS

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.

CANDIDIASIS

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

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, 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

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.

IMPAIRED HEPATIC FUNCTION

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

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

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 use machinery if these symptoms occur.

USE OF CONDOMS AND DIAPHRAGMS

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

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 human 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 **PHARMACOLOGY, Pharmacokinetics**). In view of its tumorigenic and mutagenic potential (see **Carcinogenicity/Mutagenicity**), breastfeeding is not recommended.

CARCINOGENICITY/MUTAGENICITY

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. In addition, the drug has been shown to be tumorigenic and carcinogenic in rodents. The use of metronidazole for longer treatment than usually required should be carefully weighed (see **PRECAUTIONS**) 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.

INTERACTIONS WITH OTHER MEDICINES

1. 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 hepatic metabolism. Prothrombin times should be monitored as should anticoagulant activity.
2. The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.
3. 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.
4. 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.
5. 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.
6. Carmustine, cyclophosphamide: Metronidazole should be used with caution in patients receiving these drugs.
7. There is a risk of cyclosporin serum levels increasing when it is used in combination with metronidazole. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.
8. Metronidazole used in combination with 5-fluorouracil may lead to reduced clearance of 5-fluorouracil, resulting in increased toxicity.

9. Alcoholic beverages and drugs containing alcohol should not be consumed during metronidazole therapy and for at least one day afterwards because of the possibility of a disulfiram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).
10. Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.

ADVERSE EFFECTS

No specific information is available about the suppository.

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 shocks. 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 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.

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 metronidazole 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) 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.

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.

DOSAGE AND ADMINISTRATION

A maximum of 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)

The tablets should be swallowed, without chewing, with a draught of water. It is recommended that the tablets be taken during or after a meal. Flagyl tablets may be given alone or concurrently with other bacteriologically appropriate antibacterial agents.

Treatment for 7 days should be satisfactory for most patients but, depending on clinical and bacteriological assessment, the clinician might decide to prolong treatment, e.g. for the eradication of infection from site which cannot be drained or are liable to endogenous recontamination by anaerobic pathogens from the gut, oropharynx or female genital tract.

FLAGYL

| ORAL DOSAGE | | | | | |
|----------------------------------|----------------------------|-----------------------------------|--------------------------|-------------------------|--------------------------|
| | 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 |

| ORAL DOSAGE | | | | | |
|---|-----------------------------------|--|------------------------------------|-----------------------------------|------------------------------------|
| | Duration of dosage in days | Adults and children over 12 years | Children 7-12 years | Children 3-7 years | Children 1-3 years |
| Urogenital trichomoniasis To prevent reinfection the consort should receive a similar course or treatment concurrently. | 7 or 1 | 200 mg three times daily 2g | 100 mg three times daily | 100 mg two times daily | 50 mg three times daily |
| 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 fetal 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 7 | 2 g daily 400 mg three times daily | - - | - - | - - |
| 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 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 |
| 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 |

| ORAL DOSAGE | | | | | |
|-----------------------------|----------------------------|-----------------------------------|--------------------------|------------------------|-------------------------|
| | Duration of dosage in days | Adults and children over 12 years | Children 7-12 years | Children 3-7 years | Children 1-3 years |
| 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 infection at the surgical site requires that adequate tissue concentration of the drug should have been achieved at the time of surgery. The doses and route of administration should be selected in this case to achieve this objective.

As an oral ingestion is often prohibited 12 hours or longer before surgery, and it may not be practical for a variable period following surgery, tablets are not considered to be an appropriate formulation for prophylactic use. However, if oral intake is not contraindicated and is feasible following surgery, 400 mg may be taken one to two hours before surgery and repeated every eight hours for 24 hours.

The corresponding dose for children under 12 years is 100 mg to 200 mg for 1 to 7 years, and 200 mg to 400 mg for 7 to 12 years one to two hours before surgery, repeated every eight hours for 24 hours.

SUPPOSITORIES

TREATMENT OF ANAEROBIC INFECTIONS

Adults and children over 12 years: two 500 mg suppositories inserted into the rectum every eight hours for 3 days. If the rectal medication must be continued for more than 3 days the suppositories should be inserted every twelve hours.

Children, 5 to 12 years: half the adult dosage using the 500 mg suppository.

Oral medication should be substituted as soon as possible.

PREVENTION OF ANAEROBIC INFECTIONS IN HIGH RISK SITUATIONS

A variety of dosage regimens have been tried, but the optimal variety of dosage regimen for prophylaxis against anaerobic infection still remains to be established. Based on the generally accepted principles of prophylactic use of antibiotics and the limited documented clinical experience on the prophylactic use of metronidazole, the following dosage regimens are suggested.

1. In Appendicectomy

(Note: As prevention of infection requires that adequate tissue concentrations of the drug should be achieved at the time of surgery and as it may take approximately 8 hours to achieve peak serum levels after the suppository, the need for intravenous infusion of metronidazole should be considered if the interval between the first suppository and surgery is less than 8 hours.)

Adults and children over 12 years: two 500 mg suppositories inserted into the rectum at diagnosis (ie. before surgery) and thereafter every eight hours for 48 hours after surgery.

Note: If infection has already spread, such as in cases of gangrenous or perforated appendix, the treatment regimen shown above should be used.

Children, 5 to 12 years: half the adult dosage using the 500 mg suppository.

2. In Elective Colonic Surgery

Adults and children over 12 years: In addition to proper bowel preparation, two 500 mg suppositories should be inserted every eight hours for 48 hours before as well as after surgery in cases where oral medication is not possible.

Note: Oral metronidazole should be used whenever possible due to its rapid and complete absorption. Although oral tablets and suppository have not been directly compared, peak serum levels after two 200 mg oral tablets may be expected to equal or exceed those after two 500 mg suppositories (given rectally).

Children, 5 to 12 years: 500 mg suppository should be inserted every eight hours for 48 hours before as well as after surgery in cases where oral medication is not possible.

OVERDOSAGE

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 overdoses, 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).

PRESENTATIONS AND STORAGE CONDITIONS

- Tablets:** 200 mg
Round, white to off-white tablets, one face impressed with 'MTZ 200' and a breakline on the other.
Pack sizes: 21s*.
Store below 30°C; Protect from light.
- 400 mg
Circular, white to off-white biconvex tablet, one side impressed with 'MTZ 400' and breakline on reverse.
Pack sizes: 5s, 21s*.
Store below 30°C; Protect from light.
- Suppositories:** 500 mg
Cream coloured, smooth, torpedo-shaped suppository.
Pack sizes: 10s*.
Store below 25°C.

* Marketed pack size

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia Pty Ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Tablets, Suppositories: S4

DATE OF FIRST INCLUSION IN THE ARTG

21 October 1991

DATE OF MOST RECENT AMENDMENT

15 February 2017