Name of the Drug

Metronidazole. Metronidazole is 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole. The structural formula is:

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N
O2N
\HO
\CH3
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Molecular formula: C$_6$H$_9$N$_3$O$_3$  
CAS No. 443-48-1  
Mol. Wt. 171.2

Description

Metronidazole crystals are white to brownish in colour and have a melting point of 159-162°C. A saturated solution of aqueous metronidazole has a pH of between 6 and 7.5. Solubility (g/100 mL) of metronidazole at 20°C: 1 in water; 0.5 in ethanol; 0.4 in chloroform; slightly soluble in ether; soluble in dilute acids.

Pharmacology

Pharmacokinetics

Metronidazole is readily absorbed, peak serum concentration is reached approximately 1 to 2 hour after an oral dose. Food does not significantly affect absorption and the bioavailability of the dose approaches 100% when compared with intravenous administration. Traces of metronidazole are detectable after 24 hours. Metronidazole is widely distributed in body tissues and fluids. It crosses the blood-brain barrier and the placenta. The concentration in breast milk of nursing mothers is similar to those in serum. The serum half-life of unchanged metronidazole is about 8 to 10 hours. Metronidazole is excreted in the urine as unchanged drug and its metabolites including acid oxidation products and glucuronides. Metronidazole is not protein bound to any significant degree.

Microbiology

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. Metronidazole also displays antibacterial activity against several species of anaerobic bacteria including *Bacteroides fragilis* and other species of Bacteroi, and other species such as Fusobacteria, Eubacteria, Clostridia and anaerobic Streptococci. The minimum inhibitory concentration (MIC) for most susceptible anaerobes is < 6.2 microgram/mL.

Metronidazole is inactive against aerobic and facultative anaerobic bacteria.
Indications

Metronidazole is indicated in the oral treatment of:

1. Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male. The male consort of females suffering from urogenital trichomoniasis should be treated concurrently.

2. Bacterial vaginosis.

3. All forms of amoebiasis (intestinal and extra-intestinal disease).

4. Giardiasis.

5. Acute ulcerative gingivitis.

6. Anaerobic infections including: septicaemia, bacteraemia, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis and postoperative wound infections, in which the pathogens have been identified as *Bacteroides fragilis* and other species of bacteroides, and other species such as fusobacteria, eubacteria, clostridia and anaerobic streptococci.

   Metronidazole may be used prophylactically to prevent infection by anaerobic organisms of the surgical site following appendicectomy, colonic surgery, vaginal hysterectomy, abdominal surgery in the presence of anaerobes in the peritoneal cavity and surgery performed in the presence of anaerobic septicaemia.

Contraindications

1. Patients with active organic disease of the central nervous system.

2. Evidence of, or history of blood dyscrasias, since mild leucopenia has been observed during metronidazole administration.

3. Hypersensitivity to metronidazole and other imidazoles.

Precautions

1. *Alcohol*: Alcoholic beverages and drugs containing alcohol, should not be consumed by patients being treated with metronidazole, or for at least 24 hours afterwards, as nausea, vomiting, abdominal cramps, headaches, tachycardia and flushing may occur. There is the possibility of a disulfiram-like reaction.

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

3. *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 neuropathy or central neuropathy (such as paresthesia, ataxia, dizziness, convulsive seizures). If leucopenia or abnormal neurological signs occur, the drug should be discontinued immediately.

4. *Surgical drainage*: Use of metronidazole does not obviate the need for aspiration of pus whenever indicated.

5. 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.
6. **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, resulting in plasma concentration falling below the therapeutic range. Hence a further dose of metronidazole would be needed after dialysis. 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 concentrations by high pressure liquid chromatography (HPLC) has been recommended.

7. **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. Dosage should be reduced or dosage intervals increased (see Dosage and Administration).

8. **Use 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 (see Dosage and Administration).

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

### Carcinogenesis, mutagenesis, impairment of fertility

In studies on the mutagenic potential of metronidazole, the Ames test was positive, while several nonbacterial tests in animals were negative. In 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 Precaution) and the benefit/risk ratio should therefore be carefully assessed in each case particularly in relation to the severity of the disease and the age of the patient.

### Use in Pregnancy (Risk Category: B2)

Metronidazole should not be given in the first trimester of pregnancy as it crosses the placenta and enters fetal circulation rapidly. As its effects on human fetal 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.

If a patient is treated during the 2nd or 3rd trimesters of pregnancy for urogenital trichomoniasis, the 2 g stat dose therapy should not be used as it results in higher serum levels which reach the fetal circulation.

### Use in Lactation

Metronidazole is secreted in breast milk. In view of its tumorigenic and mutagenic potential, breastfeeding is not recommended.

### Interactions with other drugs

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

**Alcohol:** Alcoholic beverages and drugs containing alcohol should not be consumed during metronidazole therapy and for at least one day afterwards because the possibility of a disulfiram-like (antabuse effect) reaction
(nausea, vomiting, tachycardia, abdominal cramps, headaches and flushing) Carmustine (BCNU) or cyclophosphamide: Metronidazole should be used with caution in patients receiving these drugs.

Lithium: 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 should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

Disulfiram: 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. Hepatic enzyme inducers: The simultaneous administration of drugs that induce microsomal hepatic enzymes, such as phenytoin or phenobarbitone, may accelerate the elimination of Metrogyl, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

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

Disulfiram: 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.

Cyclosporin: 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.

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

Effects on Laboratory tests

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

Adverse Reactions

Gastrointestinal. Metronidazole when given orally is well tolerated. Common adverse reactions refer to the gastrointestinal tract, particularly nausea, sometimes accompanied by headache, anorexia and occasionally vomiting, diarrhoea, epigastric distress and abdominal cramping; constipation and oral mucositis have been reported. A metallic, sharp, unpleasant taste is not unusual. Rare cases of pancreatitis which abated on withdrawal of the drug, have been reported. Patients with Crohn's disease 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, glossitis and stomatitis have occurred; these may be associated with a sudden overgrowth of Candida.

Body as a whole. Hypersensitivity reactions include rash, pruritus, flushing, urticaria, fever, angioedema and rare 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.

Liver. Very rare cases of reversible abnormal liver function tests and cholestatic hepatitis have been reported. Haematology. A moderate leucopenia may occur sometimes, however 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. Very rare cases of agranulocytosis, neutropenia or thrombocytopenia have been reported.

Psychiatric/central nervous system disorders. Very rare reports of encephalopathy (eg confusion) and subacute cerebellar syndrome (eg ataxia, dysarthria, gait impairment, nystagmus and tremor), which may resolve with the discontinuation of the drug. Dizziness, vertigo, incoordination and convulsive seizures have been reported. Hallucinations, irritability, depression, weakness, insomnia and a mild erythematous eruption have been experienced as have fleeting joint pains sometimes resembling serum sickness, and peripheral neuropathy characterised mainly by numbness or paraesthesia of an extremity. Since persistent peripheral neuropathy has
been reported in some patients receiving prolonged administration, 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. Transient vision disorders such as diplopia and myopia have been reported.

**Genitourinary 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 a darkened urine have been reported. The pigment which is probably responsible for this phenomenon is almost certainly a metabolite of metronidazole. It appears 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

**Summarised in table on following page.**

A maximum of 4g should not be exceeded during 24 hour period.

**Oral:**
The tablets should be swallowed, without chewing, with half a glass of water. Treatment for seven days should be satisfactory for most patients but, depending on clinical and bacteriological assessment, the clinician might decide to prolong treatment.

In patients with impaired liver function, dosage should be reduced or dosage intervals increased. Plasma metronidazole levels should be monitored (see Precautions).

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. Plasma metronidazole levels should be monitored. (see Precautions).

**Urogenital trichomoniasis.** The usual oral dosage is shown in the Table. To prevent reinfection, the partner should receive a similar course of treatment concurrently.

If treated during the second or third 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 four to six 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 retreatment.

**Note: Surgical prophylaxis**

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.

### 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 overdosages, a symptomatic and supportive treatment should be instituted.

Poison Information Centre (telephone 13 11 26) should be contacted for advice on treatment and management of overdose.
Presentation and Storage Conditions

**Metrogyl 200.** 200 mg tablet: white marked MZ on one side, G on the reverse. Each pack containing 21 tablets

**Metrogyl 400.** 400 mg tablet: yellow marked MZ on one side, G on the reverse. Each pack containing 5 or 21 tablets.

Store below 30°C

Name and Address of the Sponsor

Alphapharm Pty Limited
Chase Building 2
Wentworth Park Road
Glebe NSW 2037
ABN 93 002 359 739

Poison Schedule of the Medicine

S4

Date of Approval

Approved by the Therapeutic Goods Administration on 11 May 2000
Date of most recent amendment: 20 July 2006
<table>
<thead>
<tr>
<th>Indication</th>
<th>Duration (days)</th>
<th>Adults and children over 12 years</th>
<th>Children</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Dose</td>
<td>Doses per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>per day</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2 g</td>
<td>stat</td>
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<td>Anaerobic infections</td>
<td>7</td>
<td>400 mg</td>
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<td>Bacterial vaginosis</td>
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<td>7</td>
<td>400 mg</td>
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<td>Acute ulcerative gingivitis</td>
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<td>Amoebiasis</td>
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<tr>
<td>1. Invasive intestinal disease in susceptible individuals</td>
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<td>400 mg</td>
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<tr>
<td>3. Amoebic liver abscess and other forms of extra-intestinal amoebiasis</td>
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<td>3</td>
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<td>4. Symptomless cyst passers</td>
<td>5-10</td>
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<td>3</td>
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<tr>
<td>Surgical prophylaxis - if oral ingestion is not prohibited prior to surgery</td>
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<td>3</td>
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taken 1 to 2 hours before surgery and repeated 8 hourly for 24 hours