NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Metronidazole-AFT 500 mg/ 100 mL solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole-AFT contains metronidazole 5 mg/mL.

The product contains approximately 14 mmol of sodium ions (Na^+) per 100 mL of solution.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Intravenous infusion.

Metronidazole-AFT is a clear colourless or slightly yellowish solution with a pH between 4.5-6.0 and osmolarity of about 294 mOsm/L.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Metronidazole-AFT is indicated:

1. For treatment of anaerobic infections in patients for whom oral administration is not possible.
2. When immediate anti-anaerobic chemotherapy is required.
3. Where prophylactic cover is required at lower abdominal surgical sites presumed contaminated or potentially contaminated by anaerobic micro-organisms. Procedures of this type include 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.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Metronidazole solution for infusion is to be administered by intravenous infusion.

Dosage, rate, and duration of administration are to be individualised and depend upon the indication for use, the patient's age, weight, clinical condition, and concomitant treatment, and on the patient's clinical and laboratory response to the treatment.

Consideration should be given to official guidance on the appropriate use of antibacterial agents to reduce the development of drug resistance and maintain the effectiveness of metronidazole and other antibacterial drugs.

A maximum of 4 g should not be exceeded in a 24-hour period. For prophylactic use, the appropriate dose should be infused shortly before surgery and repeated every eight hours for the next 24 hours. 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; therefore, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

Metronidazole solution for infusion should be infused intravenously at a rate of 5 mL (25 mg) per minute. Metronidazole solution for infusion may be administered alone or concurrently (but separately) with other bacteriologically appropriate parenteral antibacterial agents. Other IV medicines or infusions should, if possible, be discontinued during its administration. While the solution should be protected from direct sunlight during administration, exposure to fluorescent light for short periods will not result in its degradation.

Adults and children over 12 years

Metronidazole solution for infusion contains 500 mg metronidazole in 100 mL and should be given by intravenous infusion every eight hours.

Children under 12 years

As for adults, but a single intravenous dose is based on 1.5 mL (7.5 mg metronidazole)/kg body weight.

Elderly

Use the adult dose with care. As some degree of hepatic or renal impairment may be present, see section 4.4.

If dilution is necessary, please refer to section “Compatibility with diluents”.

Duration of therapy

Treatment for seven days should be satisfactory for most patients but, depending upon clinical and bacteriological assessment, the clinician may decide to prolong treatment, e.g. for the eradication of infection from sites which cannot be drained or are prone to endogenous recontamination by anaerobic pathogens from the gut, nasopharynx or the female genital tract. Oral metronidazole should be substituted as soon as possible.

Administration

Product is for use in one patient on one occasion only. Discard any residue. Contains no antimicrobial preservative.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer unless the solution is clear and the seal is intact.

Do not use plastic infusion containers in series connections. This practice could result in air embolism due to air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Pressurising intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.

Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

Notes: Prevention of infection at the surgical site requires adequate tissue concentration of the medicine being attained at the time of surgery. The dose and route of administration should be selected in each case to achieve this objective.

Although metronidazole has been used in children for some years, recent evidence concerning mutagenicity and tumorigenicity suggests caution be exercised when using metronidazole in this age group.

If dilution is required in infants or other patients maintained on intravenous infusions, please refer to Section 6.6, heading "Compatibility with diluents".

4.3 CONTRAINDICATIONS

Metronidazole-AFT is contraindicated:

1. in 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.
2. in patients with evidence of, or a history of, blood dyscrasias. (Occasionally a mild leucopenia has been observed during administration; however no persistent haematological abnormalities have been observed in animals or clinical studies.)
3. in the presence of active organic disease of the central nervous system.
4. in patients who are hypersensitive to metronidazole or other imidazole derivatives or any of the excipients (see section 6.1).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Central and peripheral nervous system effects

Metronidazole should be used with caution in patients with active or chronic severe peripheral or central nervous system diseases due to the risk of neurological damage. Patients should be warned about the potential for confusion, hypoacusis, dizziness, hallucinations, convulsions or transient visual disorders.

Severe neurological disturbances (including seizures and peripheral and optic neuropathies) have been reported in patients treated with metronidazole. Stop metronidazole treatment if any abnormal neurologic symptoms occur such as ataxia, dizziness, confusion or any other CNS adverse reaction.

Cases of encephalopathy and peripheral neuropathy (including optic neuropathy) have been reported with metronidazole. Encephalopathy has been reported in association with cerebellar toxicity characterised by ataxia, dizziness and dysarthia and accompanied by CNS lesions seen on magnetic resonance imaging (MRI). CNS symptoms and CNS

lesions are generally reversible within days to a week upon discontinuation of metronidazole.

Peripheral neuropathy, mainly of sensory type, has been reported and is characterised by numbness or paraesthesia of the extremities.

Convulsive seizures have been reported in patients treated with metronidazole.

Aseptic meningitis

Cases of aseptic meningitis have been reported with metronidazole. Symptoms can occur within hours of dose administration and generally resolve after discontinuation of the metronidazole therapy, see section 4.8.

The appearance of abnormal neurological signs demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

Candidiasis

Fungal overgrowth of the gastrointestinal or genital tract may occur during the metronidazole therapy and require treatment with a candicidal medicine.

Regular monitoring

Regular clinical and laboratory monitoring (including blood count) are advised in cases of high-dose, prolonged, or repeated treatment as the risk for adverse reactions is increased.

Long-term therapy

If metronidazole is administered for more than ten 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. If leucopenia or abnormal neurological signs occur, the medicine should be discontinued immediately.

Surgical drainage

Use of metronidazole does not obviate the need for drainage of pus whenever indicated such as in amoebic liver abscess or abscess in other accessible positions.

Sodium retention

Care should be taken because of the sodium content (see Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION) in this dosage form.

Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administrating Metronidazole-AFT to patients on a controlled sodium diet, patients receiving corticosteroids or patients predisposed to oedema, see section 4.5.

Alcohol

Discontinue consumption of alcoholic beverages or alcohol-containing products before, during, and up to 72 hours after taking metronidazole because abdominal cramps, nausea, vomiting, flushing, headaches, and tachycardia may occur, see section 4.5.

Pseudomembranous colitis

Pseudomembranous colitis associated with the administration of metronidazole has been reported.

Ototoxicity

A number of cases of deafness associated with the use of metronidazole have been reported.

History of blood dyscrasia

Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or a history of, blood dyscrasia. Leucopenia, agranulocytosis and neutropenia have been observed during metronidazole administration, however no persistent haematological abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leucocytes counts are recommended before and after therapy.

Use in hepatic impairment

Since metronidazole is mainly metabolised by hepatic oxidation, accumulation of metronidazole and its metabolites in plasma is likely in patients with severely impaired hepatic function. Metronidazole should therefore be administered with cautions and at reduced doses to patients with severe hepatic impairment.

Use with caution in patients with hepatic encephalopathy. Patients with severe hepatic encephalopathy metabolise metronidazole slowly, with resultant accumulation of metronidazole. This may cause exacerbation of CNS adverse effects. Reduce the dose of metronidazole as necessary.

Use in renal impairment

Use with caution in patients with severe renal impairment. Dose adjustment may be necessary.

In patients being haemodialysed twice weekly, metronidazole and its major metabolite are rapidly removed during an eight-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 2-hydroxymethyl metabolite could be associated with side effects and measurement of its plasma concentration by high pressure liquid chromatography (HPLC) has been recommended.

In the absence of haemodialysis, the plasma clearance and elimination half-life of metronidazole are equivalent to those in patients with normal renal clearance, so dosage adjustment is not necessary.

Patients with severe renal impairment who are not undergoing haemodialysis should have their blood metronidazole and metronidazole metabolite levels monitored; monitor for signs of toxicity.

Patients receiving peritoneal dialysis should be monitored for signs of toxicity due to the potential accumulation of metronidazole metabolites.

While the pharmacokinetics of metronidazole are little changed in the anuric patient, the metabolites are retained; the clinical significance of this is unknown.

Use in the elderly

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy, see section 4.2.

Paediatric use

No data available.

Effects on laboratory tests

Metronidazole may interfere with AST (SGOT), ALT (SGPT), LDH, triglycerides, or glucose determinations when these are based on the decrease in ultraviolet absorbance which occurs when NADH is oxidised to NAD. Metronidazole interferes with these assays because the drug has an absorbance peak of 322 nm at pH 7 which is close to the 340 nm absorbance peak of NADH; this causes an increase in absorbance at 340 nm resulting in falsely decreased values.

Instructions to be given to the patient

1. Patients, especially pregnant women, should be warned to refrain from alcohol whilst taking metronidazole.
2. Patients should be advised to report any signs of toxicity, especially neurological disturbances, to their doctor.
3. Patients should be warned about the possibility of their urine darkening in colour.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Warfarin and other coumarin anticoagulants

Oral or IV metronidazole potentiates the effects of oral anticoagulants resulting in prolongation of prothrombin time and increased risk of haemorrhages; concurrent administration should be avoided if possible. If metronidazole is used in patients receiving an oral anticoagulant, prothrombin times and international normalised ratio (INR) should be carefully monitored, and the dosage of the anticoagulant adjusted accordingly. Monitor patients for signs and symptoms of bleeding.

Alcohol

Metronidazole appears to inhibit alcohol dehydrogenase and other alcohol oxidising enzymes. Mild disulfiram-like reactions including flushing, headache, nausea, vomiting, abdominal cramps, sweating and tachycardia have occurred in patients ingesting alcohol while being treated with metronidazole.

Patients should be advised not to take alcohol-containing products before, during and up to 72 hours after metronidazole therapy because of the possibility of a disulfiram-like reaction.

Disulfiram

Administration of disulfiram with metronidazole has been associated with acute psychoses and confusion in some patients; therefore, the two medicines should not be administered concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.

Lithium

Concomitant use of lithium and metronidazole decreases lithium clearance which may result in lithium toxicity. Lithium toxicity may lead to renal damage. Frequent monitoring of serum lithium and creatinine levels is necessary.

Initiation of short-term metronidazole therapy in patients stabilised on a relatively high dosage of lithium has been reported to increase serum lithium concentrations, resulting in signs of lithium toxicity in several patients. Serum lithium and serum creatinine levels should be obtained several days after commencing metronidazole therapy to detect any increase that may precede clinical symptoms of lithium intoxication.

Corticosteroids

Care should be taken when administering metronidazole infusion to patients receiving corticosteroid therapy or to patients predisposed to oedema since administration of solutions containing sodium ions may result in sodium retention.

Cyclophosphamide and carmustine (BCNU)

Metronidazole should be used with caution in patients who are receiving cyclophosphamide or carmustine as a drug interaction demonstrated in mice leads to increased toxicity.

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 co-administration is necessary.

Fluorouracil and azathioprine

Transient neutropenia has been reported in 12 patients who received oral and IV metronidazole in conjunction with IV fluorouracil and in at least one patient who received oral metronidazole in conjunction with azathioprine.

5-Flourouracil

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

Busulfan

Metronidazole may increase plasma concentrations of busulfan, which may result in an increased risk for serious busulfan toxicity such as sinusoidal obstruction syndrome, gastrointestinal mucositis, and hepatic veno-occlusive disease.

Cytochrome P450 inhibitors

Simultaneous administration of medicines that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease the plasma clearance of metronidazole which may result in metronidazole toxicity. It is not clear if ranitidine exerts a similar effect.

Cytochrome P450 inducers

The simultaneous administration of medicines which induce microsomal liver enzyme activity, such as phenobarbital, pentobarbital and phenytoin may accelerate the elimination of metronidazole, resulting in reduced plasma concentrations and increased concentrations of its 2-hydroxymethyl metabolite; impaired clearance of phenytoin has also been reported.

Cytochrome P450 3A4 (CYP3A4) substrates

Concomitant use of metronidazole and CYP3A4 substrates (e.g., amiodarone, tacrolimus, cyclosporin, carbamazepine, and quinidine) may increase respective CYP3A4-substrate plasma levels. Monitoring of plasma concentrations of CYP3A4 substrates may be necessary.

Vecuronium

Metronidazole may potentiate the effects of vecuronium.

See also Section 6.2 for incompatibilities.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy - Category B2

There is no adequate data on the use of metronidazole in pregnant women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing metronidazole.

Metronidazole should not be given in the first trimester of pregnancy since it crosses the placenta and rapidly enters the foetal circulation. 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.

Australian categorisation definition of Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Breast-feeding

There is no adequate data on the use of metronidazole in lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing metronidazole.

Metronidazole is secreted in breast milk. In view of the tumorigenic and mutagenic potential, breast-feeding is not recommended. During lactation, either breastfeeding or metronidazole should be discontinued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Some adverse reactions to metronidazole such as seizure, dizziness, optic neuropathy, may impair the ability to drive or operate machines, see section 4.8. 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.

4.8 UNDESIRABLE EFFECTS

When administered intravenously, metronidazole is well tolerated.

Gastrointestinal disorders

The most common adverse reactions have involved the gastrointestinal tract and include nausea, vomiting, diarrhoea, epigastric distress and abdominal pain, cramping, constipation and oral mucositis. A metallic, sharp unpleasant taste is not unusual. Tongue discolouration and dry mouth have been reported. Furry tongue, glossitis and stomatitis have occurred; these may be associated with *Candida* overgrowth. Proliferation of *Candida* may also occur in the vagina.

Rare cases of pancreatitis, abating on withdrawal of the medicine, have been reported.

There have been a number of reports in overseas literature of cases of pseudomembranous colitis whilst on metronidazole therapy.

Blood and lymphatic system disorders

A moderate and transient leucopenia may occasionally be observed. If this occurs, the total leucocyte count may be expected to return to normal after the course of medication is completed. Reversible thrombocytopenia and thrombophlebitis have been reported rarely.

Very rare cases of bone marrow aplasia, agranulocytosis and neutropenia have been reported. Eosinophilia has also been reported.

Nervous system disorders

The most serious adverse reactions in patients treated with metronidazole injection have been convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy. Lack of coordination, hypoacusis and ataxia have been reported. Confusion, irritability, depression, weakness, and insomnia have been experienced as has peripheral neuropathy, characterised mainly by numbness or paraesthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged metronidazole therapy, such subjects should be specifically warned about these reports and told to stop the medicine and report immediately if any neurological symptoms occur. Transient vision disorders such as diplopia and myopia, headache, dizziness, syncope, dysarthria, somnolence, hypoesthesia and dysgeusia have also been reported.

Psychiatric disorders

Depression, confusional state and insomnia have been reported. Psychotic reactions have been reported in alcoholic patients receiving metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram in the previous two weeks.

Hepatobiliary disorders

Very rare cases of reversible abnormal liver function tests and cholestatic hepatitis have been reported. Jaundice has also been reported.

Auditory and vestibular disorders

Dizziness, vertigo, hypoacusis and tinnitus have been reported.

Skin and subcutaneous disorders

Erythematous rash, pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome, fixed eruption, swelling face, urticaria, hyperhidrosis, erythema and rash have been reported.

Immune system disorders

Anaphylactic reaction and hypersensitivity have been reported. Urticaria, erythematous rash, Stevens-Johnson Syndrome, flushing, nasal congestion, dryness of mouth (or vagina or vulva), fever, angiooedema and rare anaphylactic shock have been reported.

Musculo-skeletal and connective tissue disorders

Fleeting joint pains sometimes resembling “serum sickness”, muscle spasms, arthralgia and myalgia have been reported.

Renal and urinary disorders

Dysuria, cystitis, chromaturia and a sense of pelvic pressure have been reported. Very rarely, dyspareunia, fever, polyuria, incontinence, decrease in libido, proctitis and pyuria

have occurred in patients receiving the medicine. Instances of darkened urine have been reported and this manifestation has been the subject of investigation. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it almost certainly is 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.

Eye disorders

Optic neuropathy has been reported.

Cardiac disorders

Flattening of the T-wave and prolongation of the QT interval may be seen in ECG tracings. Tachycardia and palpitations have been reported.

Metabolism and Nutritional disorders

Decreased appetite has been reported.

Respiratory, thoracic and mediastinal disorders

Dyspnoea has been reported.

General disorders and administration site conditions

Injection site reaction, malaise, face oedema, oedema peripheral, chest pain, chills, asthenia have been reported.

Investigations

Hepatic enzyme increase has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at: https://pophealth.my.site.com/carmreportnz/s.

4.9 OVERDOSE

Overdosage with metronidazole appears to be associated with very few abnormal signs or symptoms. Signs and symptoms of an overdose may include: nausea, vomiting, and neurotoxic effects, including ataxia, confusion, disorientation, seizures, and peripheral neuropathy. Disorientation and vomiting may occur, especially after ingestion of large amounts.

The effects of an overdose may require immediate medical attention and treatment. There is no specific antidote for an overdose of metronidazole. Symptomatic treatment is recommended. Discontinue metronidazole administration in the event of an overdose. In the event of accidental overdosage, treatment consisting of supportive and symptomatic measures is recommended.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON].

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group

Antibacterials for systemic use: imidazole derivatives; ATC code: J01XD01

and

Antiprotozoals: nitroimidazole derivatives; ATC code: P01AB01

Classification of activity

Metronidazole is a nitroimidazole anti-infective agent which has specific activity against a number of obligate anaerobic organisms and protozoa.

Microbiology

Metronidazole is bactericidal *in vitro* against many anaerobic Gram-negative bacilli including *Bacteroides fragilis* and other *Bacteroides* species; also other species including *Fusobacterium*. The medicine is effective against many anaerobic Gram-positive bacilli including *Clostridium* species, *Eubacterium*, and anaerobic *Streptococcus*. The MIC for most susceptible anaerobes is < 6.2 micrograms/mL. Serum levels higher than this are achieved at the recommended doses.

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

Metronidazole is ineffective against both aerobic and facultative anaerobic bacteria.

Susceptibility tests

Dilution or diffusion techniques, either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Mechanism of action

Metronidazole is bactericidal, amoebicidal and trichomonicidal. The exact mode of action has not been fully elucidated. Metronidazole is reduced by low-redox-potential electron transfer proteins (e.g. nitro-reductases such as ferredoxin) to unidentified polar product(s) which lack the nitro group. The reduction product(s) appears to be responsible for the cytotoxic and antimicrobial effects of the medicine which include disruption of DNA and inhibition of nucleic acid synthesis.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Bioavailability

For both oral and intravenous administration, the area under the plasma clearance curve is equivalent.

Absorption

Maximum plasma concentrations occur at the conclusion of the infusion after intravenous administration. Traces are detected after 24 hours. The biological half-life of a single intravenously administered dose of metronidazole has been determined as 7.3 hours ± 1.0 hours.

Distribution

Metronidazole is widely distributed in body tissues and fluids. It diffuses across the blood-brain barrier, crosses the placenta and appears in the saliva and breast milk of nursing mothers in concentrations equivalent to those found in the plasma. It attains therapeutic concentrations in the bile and the CSF.

Plasma protein binding

Metronidazole is not significantly bound to plasma protein.

Metabolism

An oral or intravenous dose of metronidazole is partially metabolised in the liver by hydroxylation, acid side-chain oxidation and glucuronide conjugation. The major metabolite, 2-hydroxymethyl metronidazole, has some antiprotozoal activity *in vitro*.

Excretion

Approximately three-fourths of a single 750 mg oral dose is excreted as nitro-containing compounds (unchanged medicine and its metabolites) in the urine within 5 days. Most of the remainder is excreted in the faeces. Urine may be dark or reddish brown in colour following oral and IV administration of the medicine due to the presence of water-soluble pigments, which result from its metabolism.

Note: Polarographic estimation of metronidazole in serum or urine tends to give higher values than microbiological assay because the former measures unchanged drug and metabolites, erroneously high serum values may be obtained in the presence of severe renal failure because of the retention of metabolites in the blood.

5.3 PRECLINICAL SAFETY DATA

Mutagenicity, tumorigenicity

In studies on the mutagenic potential of metronidazole, the Ames mutagenicity test was positive, while several nonbacterial tests in animals were negative. In patients suffering from Crohn's Disease, metronidazole increased chromosome abnormalities. In addition, the medicine has been shown to be tumorigenic in rodents. 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.

Genotoxicity

No data available

Carcinogenicity

Metronidazole has been shown to be carcinogenic in rats and mice. Its use therefore should be reserved for the conditions listed in the indications section.

Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic oral administration in mice and rats. Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in multiple studies, including one in which the animals were dosed on an intermittent schedule (every fourth week only). The results of one of the mouse studies indicates a statistically significant increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding.

In the rat, there was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumours, among females fed metronidazole on a lifetime basis, over that observed in concurrent female control groups.

Two lifetime tumorigenicity studies have been performed in hamsters; in both cases the results were negative.

A retrospective study of 771 women treated with metronidazole for *Trichomonas vaginalis* has revealed no statistically significant increase in cancer incidence over that expected in the normal population. An apparent increase in the incidence of cervical carcinoma observed in the metronidazole-treated group was no different from the incidence observed in women documented to have had trichomoniasis not treated by metronidazole.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride

Disodium phosphate dodecahydrate

Citric acid monohydrate

Water for injections

6.2 INCOMPATIBILITIES

Metronidazole solution for infusion is incompatible with aluminium; do not use equipment containing aluminium components (e.g., needle or cannula hubs). Other medicines should not be added directly to Metronidazole solution for infusion.

6.3 SHELF LIFE

30 months.

From microbiological point of view, the diluted solution must be used immediately after preparation. However, if storage is necessary, the diluted solutions can be stored at room temperature (below 25 °C) for not more than 6 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C. For storage conditions after dilution of the medicine, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Polypropylene bottles. Pack of 40 bottles.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

Compatibility with diluents

Metronidazole-AFT (100 mL) may be diluted with 500 mL of 0.9% sodium chloride solution, 5% glucose solution, glucose-saline combination (250 mL of 5% glucose solution for infusion + 250 mL of sodium chloride 0.9% solution for infusion), potassium chloride injection 20 mmol or potassium chloride injection 40 mmol.

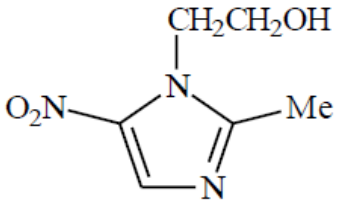
Contains no antimicrobial preservative. Product is for use in one patient on one occasion only. Discard any residue.

For storage conditions after dilution of the medicine, see section 6.3.

6.7 PHYSICOCHEMICAL PROPERTIES

Metronidazole is a white or yellowish crystalline powder with melting point 159 – 162 °C. Solubility in water at 20 °C is 1 g/100 mL; in ethyl alcohol, 0.5 g/100 mL; in chloroform, 0.4 g/100 mL; slightly soluble in ether and soluble in dilute acids.

Chemical structure



Chemical name: 2-(5-nitro-2-methylimidazol-1-yl) ethanol

Molecular Formula: $C_6H_9N_3O_3$

Molecular Weight: 171.2

CAS number

443-48-1

7 MEDICINE SCHEDULE

Prescription only medicine

8 SPONSOR

AFT Pharmaceuticals Pty Ltd.
Auckland

Email: customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

29 October 2026

10 DATE OF REVISION

Not applicable

Summary table of changes

Section changed	Summary of new information