AUSTRALIAN PRODUCT INFORMATION – METRONIDAZOLE INTRAVENOUS INFUSION (Metronidazole)

1. NAME OF THE MEDICINE

Metronidazole

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole Intravenous Infusion contains metronidazole 5 mg/mL.

It is a white or yellowish, crystalline powder, slightly soluble in water, in acetone, in alcohol and in methylene chloride.

Metronidazole Intravenous Infusion is a clear, almost colourless to pale yellow, sterile, isotonic, preservative-free, ready to use solution. Each mL contains 0.135 mmoles sodium.

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

3. PHARMACEUTICAL FORM

Intravenous Infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of severe anaerobic infection when oral medication is not possible or is contraindicated, when immediate anti-anaerobic therapy is required.

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.

4.2 Dose and method of administration

Metronidazole Intravenous Infusion contains no microbial agent. It should be used in one patient on one occasion only and any residue discarded.

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

Dosage

Adult: The adult dose is 500 mg metronidazole (*i.e.*, 100 mL) by infusion eight hourly.

Children over 12 years: Same dosage as adults.

Children under 12 years: Eight hourly as for adults but the single intravenous dose is based on 7.5 mg (1.5 mL) metronidazole/kg bodyweight.

Geriatric: Use adult dosage with care as some degree of impaired hepatic or renal function may be present in elderly patients. In elderly patients, the pharmacokinetics of metronidazole may be altered; therefore, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

Method of administration

Single use only.

Metronidazole should be infused intravenously at the rate of 5 mL (25 mg) per minute. Metronidazole infusion may be administered alone or concurrently (but separately) with other appropriate antibacterial agents in parenteral dosage forms (see Section 6.2 Incompatibilities). Other intravenous drugs or infusions should, if possible, be discontinued during its administration.

For prophylactic use the appropriate dose should be infused shortly before surgery and repeated 8 hourly 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 metronidazole dosage accordingly.

Parenteral drugs should be inspected visually for particulate matter and discolouration prior to administration, wherever solution or container permits. Do not use if the solution is cloudy or precipitated or if the seal is not intact. While the solution should be protected from direct sunlight during administration, exposure to fluorescent light for short periods will not result in its degradation.

Do not use plastic infusion bags 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.

Duration of therapy: Treatment for seven 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 sites which cannot be drained or are liable to endogenous recontamination by anaerobic pathogens from the gut, oropharynx or female genital tract. Oral medication should be substituted as soon as possible.

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.

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

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

Additional information: Metronidazole Intravenous Infusion is an isotonic (280 mOsm per kg), ready to use solution, requiring no dilution or buffering prior to administration.

The total sodium content (derived from sodium phosphate buffer and sodium chloride) is approximately 13.5 mmol (13.5 mEq, 310 mg) per 100 mL of solution. This must be considered in patients on a restricted sodium intake when calculating total daily sodium intake.

Dosage Adjustments

Renal Impairment

In patients on twice weekly haemodialysis, metronidazole and its major active metabolite are rapidly removed during an 8-hour period of dialysis, so 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 concentrations by high pressure liquid chromatography (HPLC) has been recommended.

While the pharmacokinetics of metronidazole are little changed in the presence of anuria, there is retention of the metabolites, the clinical significance of which is unknown.

Hepatic Impairment

As metronidazole is partly metabolised in the liver, caution should be exercised in patients with impaired liver function. Empirical dosage reduction and serum level monitoring may be necessary.

4.3 Contraindications

1. Patients with evidence of or a history of blood dyscrasias should not receive the drug since upon occasion a moderate leucopenia has been observed during its administration. However, no persistent haematological abnormalities have been observed in animals or clinical studies (see Section 4.4 Special warnings and precautions for use).

2. Active organic disease of the central nervous system.

3. Hypersensitivity to metronidazole and other nitroimidazoles.

4. Patients who have taken disulfiram within the last two weeks should not be administered metronidazole. Use of oral metronidazole is associated with psychotic reactions in alcoholic patients who were using disulfiram concurrently (see Section 4.5 Interactions with other medicines and other forms of interactions).

5. Consumption of alcohol or products containing propylene glycol. Use of oral metronidazole is associated with a disulfiram-like reaction to alcohol, including abdominal cramps, nausea, vomiting, headaches, and flushing. Discontinue consumption of alcohol or products containing propylene glycol during and for at least three days after therapy with metronidazole (see Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions).

6. Metronidazole Intravenous Injection is contraindicated 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 (see Section 4.8 Adverse effects (undesirable effects)).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Hypersensitivity reactions including severe cutaneous adverse reactions (SCARs) can be serious and potentially life threatening (see Section 4.8 Adverse effects (undesirable effects)).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported with the use of metronidazole. Symptoms can be serious and potentially life threatening. If symptoms or signs of SCARs develop, discontinue Metronidazole Intravenous Infusion immediately and institute appropriate therapy.

Advise patients that metronidazole injection may increase the risk of serious and sometimes fatal dermatologic reactions, including TEN, SJS, and DRESS. Instruct the patient to be alert for skin rash, blisters, fever or other signs and symptoms of these hypersensitivity reactions. Advise patients to stop Metronidazole Intravenous Infusion immediately if they develop any type of rash and seek medical attention.

Alcohol

Alcoholic beverages, drugs containing alcohol or products containing propylene glycol should not be consumed by patients being treated with metronidazole and for at least three days after treatment as nausea, vomiting, abdominal cramps, headaches, tachycardia and flushing may occur. There is the possibility of a disulfiram-like reaction (see Section 4.3 Contraindications).

Treatment of bacterial infections

Patients should be counselled that antibacterial drugs including Metronidazole Intravenous Infusion should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Metronidazole Intravenous Infusion is prescribed to treat a

bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be completed for the full course of therapy. Otherwise, this may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Metronidazole Intravenous Infusion or other antibacterial drugs in the future.

Candidiasis

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

Use in patients with blood dyscrasias

Metronidazole is a nitroimidazole and should be used with care in patients with evidence of or history of blood dyscrasia. A moderate leucopenia has been observed during its administration; however, no persistent haematologic abnormalities attributable to metronidazole have been observed in clinical studies (see Section 4.3 Contraindications).

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 paraesthesia, ataxia, dizziness, convulsive seizures). If leucopenia or abnormal neurological signs occur, the drug should be discontinued immediately.

Cardiac function impairment

Care should be taken because of the sodium content (0.135 mmol/mL) in this dosage form.

Sodium retention

Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administering Metronidazole Intravenous Infusion to patients receiving corticosteroids or patients predisposed to oedema.

Surgical drainage

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

Nervous system

Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological damage. Patients should be warned about the potential for confusion, dizziness, hallucinations, convulsions or transient visual disorders and advised not to drive or use machinery if these symptoms occur.

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 dysarthria. CNS lesions seen on MRI have been described in reports of

encephalopathy. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible.

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

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 metronidazole therapy is discontinued.

The appearance of abnormal neurologic signs demands prompt discontinuation of metronidazole therapy and, when severe, immediate medical attention. See Section 4.8 Adverse effects (undesirable effects).

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 Section 4.2 Dose and method of administration) 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.

Drug resistant bacteria

Prescribing metronidazole in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Use in renal impairment

In patients on twice weekly haemodialysis, metronidazole and its major active metabolite are rapidly removed during an 8-hour period of dialysis, so that the plasma concentration quickly falls below the therapeutic range. Hence, a further dose of metronidazole would be needed after dialysis to restore an adequate plasma concentration. In patients with renal failure the half-life of metronidazole is unchanged, but those of its major metabolites are prolonged 4-fold or greater. The accumulation of the hydroxy metabolite could be associated with side effects and measurement of its plasma concentration by high pressure liquid chromatography (HPLC) has been recommended (see Section 4.2 Dose and method of administration).

Use in hepatic impairment

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

For patients with severe hepatic impairment (Child-Pugh C), a reduced dose of metronidazole is recommended. For patients with mild to moderate hepatic impairment, no dosage adjustment

is needed but these patients should be monitored for metronidazole associated adverse events (see Section 4.2 Dose and method of administration).

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.

Use in the elderly

See Section 4.2 Dose and method of administration.

Paediatric use

See Section 4.2 Dose and method of administration.

Effects on laboratory tests

Metronidazole may show negative interference with continuous flow spectrophotometry of aspartate aminotransferase (previously GOT), so that hepatocellular damage which is detectable by raised serum AST may be missed. 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 nanometres at pH 7, which is close to the 340 nanometre absorbance peak of NADH; this causes an increase in absorbance at 340 nanometres resulting in falsely decreased values.

4.5 Interactions with other medicines and other forms of interactions

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. Disulfiram: In a clinical trial of combined therapy with disulfiram and metronidazole in the treatment of chronic alcoholics, severe acute psychotic reactions occurred in 6 out of 29 patients. 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 (see Section 4.3 Contraindications).

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

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

8. Fluorouracil and azathioprine: Transient neutropenia has been reported in twelve patients who received oral and intravenous metronidazole in conjunction with intravenous fluorouracil and in at least one patient who received oral metronidazole in conjunction with azathioprine.

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

10. Alcoholic beverages, drugs containing alcohol or products containing propylene glycol should not be consumed during metronidazole therapy and for at least three days afterwards because of the possibility of a disulfiram-like reaction (flushing, vomiting, tachycardia). See Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use.

11. Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity. Metronidazole should not be administered concomitantly with busulfan unless the benefit outweighs the risk. If no therapeutic alternatives to metronidazole are available, and concomitant administration with busulfan is medically needed, frequent monitoring of busulfan plasma concentration should be performed and the busulfan dose should be adjusted accordingly.

12. 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.

13. Drugs that prolong the QT interval: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy - Category B2

Metronidazole should not be given in the first trimester of pregnancy as it crosses the placenta and enters 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.

Use in lactation

Metronidazole is secreted in breast milk (see Section 5.2 Pharmacokinetic properties). There are reports of diarrhoea and *Candida* infection in breastfed infants of mothers receiving treatment with metronidazole.

There are no data on the effects of metronidazole on milk production.

Animal studies have shown the potential for tumorigenicity after oral metronidazole was administered chronically to rats and mice (see Section 4.4 Special warnings and precautions for use: Carcinogenicity/Mutagenicity). In view of its tumorigenic and mutagenic potential (see Section 4.4 Special warnings and precautions for use: Carcinogenicity/Mutagenicity), breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines

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 (see Section 4.4 Special warnings and precautions for use).

4.8 Adverse effects (undesirable effects)

When administered intravenously, metronidazole is well tolerated.

Gastrointestinal

The most common adverse reactions have involved the gastrointestinal tract and include vomiting, diarrhoea, epigastric distress, abdominal cramping, constipation and oral mucositis.

A metallic, sharp unpleasant taste is not unusual. Furry tongue, glossitis and stomatitis have occurred; these may be associated with *Candida* overgrowth.

Patients with Crohn's disease are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established.

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

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

Body as a whole

Hypersensitivity reactions include erythematous rash, pruritus, flushing, urticaria, fever, angioedema and anaphylactic shock. Nasal congestion and dryness of the mouth have been reported. Mild erythematous eruptions have been experienced, as have fleeting joint pains sometimes resembling serum sickness. Pustular eruptions and acute generalised exanthematous pustulosis have been reported. Dermatitis bullous and fixed drug eruption have been reported. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised

exanthematous pustulosis (AGEP) have also been reported (see Section 4.4 Special warnings and precautions for use).

Liver

Increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice, have been reported.

Cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs; all spiramycin except one case of tetracycline.

Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (latency from drug start to signs of liver failure as short as 2 days) (see Section 4.3 Contraindications).

Haematology

A moderate leucopenia may be observed occasionally. If this occurs, the total leucocyte count may be expected to return to normal after the course of medication is completed. One case of bone marrow depression has been reported. If profound bone marrow suppression occurs, use of metronidazole should be ceased and appropriate supportive therapy instituted. Cases of agranulocytosis, neutropenia or thrombocytopenia have been reported.

Thrombophlebitis has been reported after intravenous infusion. This reaction can be minimised or avoided by limiting the duration of infusion and frequent resting of the indwelling IV cannula.

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 the 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

QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval. Flattening of the T wave may be seen in ECG tracings.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

Signs and 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.

Recommended 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).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Specific bactericidal activity against important obligate anaerobes.

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

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

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

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Note: Polarographic estimation of metronidazole in serum or urine tends to give higher values than microbiological assay because the former measures both 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.

Absorption

Following intravenous infusion, peak plasma levels of metronidazole occur at the end of the infusion.

Distribution

Metronidazole is distributed widely throughout body tissues both intracellularly and extracellularly. It is found in saliva and breast milk in concentrations equivalent to those in plasma. It also crosses the placenta and is found in the CSF. Therapeutic levels have been found in abscesses, bile, CSF, seminal fluid and in synovial fluid.

Protein binding

There is no significant plasma protein binding of metronidazole.

Metabolism

Metronidazole is partly metabolised in the liver by both acid oxidation and glucuronide conjugation. The principal metabolites are the hydroxy metabolite (1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole) and the acid metabolite (1-acetic acid-2-methyl-5-nitroimidazole). The hydroxy metabolite has approximately 30% of the bioactivity of metronidazole against anaerobic bacteria whereas the acid metabolite has only 5% of the activity of unchanged metronidazole.

Excretion

About 15 to 20% of an administered dose is excreted in the urine as unchanged metronidazole. Overall, about 50-80% of an administered dose is excreted as nitro- containing compounds, of which unchanged metronidazole and the hydroxymethyl homologue each account for about one third. The fate of the remainder of an administered dose is unknown. Metronidazole is also excreted into saliva and breast milk reaching concentrations equivalent to those in plasma.

Half life

The half life of metronidazole after single, intravenous infusion has been reported as 7.3 ± 1.0 hours.

5.3 Preclinical safety data

Genotoxicity

Refer to Section 4.4 Special warnings and precautions for use: Carcinogenicity/Mutagenicity.

Carcinogenicity

Refer to Section 4.4 Special warnings and precautions for use: Carcinogenicity/Mutagenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid

Dibasic sodium phosphate

Sodium chloride

Water for injections

6.2 Incompatibilities

Additives should not be introduced into intravenous metronidazole solutions. If used with a primary intravenous fluid system, the primary solution should be discontinued during metronidazole infusion.

6.3 Shelf life

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

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

AUST R 12728 Metronidazole Intravenous Infusion 500 mg in 100mL (sterile) plastic* or glass vial.

Pack sizes of 1* and 10 vials.

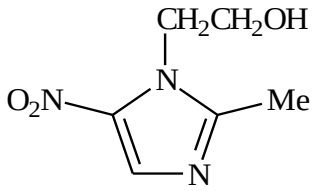
*Note: * not marketed*

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

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 (POISONS STANDARD)

Prescription only medicine (S4)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

13 August 1991

10. DATE OF REVISION

12 September 2024

Summary Table of Changes

Section changed	Summary of new information
Throughout	Minor editorial changes.
4.4	Addition of warning on severe cutaneous adverse reactions (SCARs)