AUSTRALIAN PRODUCT INFORMATION- METRONIDAZOLE KABI (METRONIDAZOLE)

1 NAME OF THE MEDICINE

Metronidazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole Kabi contains the active substance metronidazole, which belongs to the substance group of nitroimidazole derivatives.

Active: metronidazole, concentration: 500 mg/100 mL

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; and soluble in dilute acids. When reconstituted as Metronidazole Kabi, it has a pH of between 4.5 and 6.0. Each mL contains 0.135 mmol sodium.

Metronidazole Kabi is a clear and slightly yellowish, sterile, isotonic infusion solution for intravenous use only. Solution is practically free from visible particles. Solutions that are hazy or contain visible particulate matter should be discarded.

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

Metronidazole intravenous infusion is indicated:

(a) for treatment of anaerobic infections in patients for whom oral administration is not possible.

(b) where immediate anti-anaerobic chemotherapy is required.

(c) where prophylactic cover is required at lower abdominal surgical sites presumed contaminated or potentially contaminated by anaerobic micro-organisms. Procedures of this type 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 or facultative anaerobic bacteria.

4.2 DOSE AND METHOD OF ADMINISTRATION

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.

Metronidazole should be infused intravenously at a rate of 5 mL (25 mg) per minute. Metronidazole infusion may be administered alone or concurrently (but separately) with other bacteriologically appropriate parenteral antibacterial agents. Other IV drugs 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: 100 mL containing 500 mg metronidazole 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. In elderly patients, the pharmacokinetics of metronidazole may be altered; therefore, monitoring of serum levels may be necessary to adjust metronidazole dosage accordingly.

If dilution is necessary, hold at 2° to 8°C for not more than 24 hours to reduce microbiological hazard.

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

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: One dose in one patient only. Discard any remaining contents.

Notes: Prevention of infection at the surgical site requires adequate tissue concentration of the drug 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.

In infants and other patients maintained on intravenous infusions, metronidazole may be diluted 1 in 5 or greater with isotonic intravenous infusions (Sodium Chloride 0.9%, Glucose-saline combinations, Glucose 5%) but not Sodium Lactate Compound (Hartmann's) Infusion or Sodium Chloride Compound (Ringer's) Infusion (see **Section 4.5 Interactions with other medicines and other forms of interactions – Compatibility with intravenous infusions and other drugs).**

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. I 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 or any of the excipients.

(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 infusion 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 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 [see **Section 4.8 Adverse effects (undesirable effects)**].

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 (Antabuse) effect 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 of 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 hematologic 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 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 (such as paresthesia, 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 Kabi to patients receiving corticosteroids or patients predisposed to oedema. (Refer to **Section 4.5 Interactions with other medicines and other forms of interactions**).

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 in patients being treated 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 the 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 and symptoms 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 4.4 Special warnings and precautions for use**) 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

Refer to **Section 4.2 Dose and method of administration.**

Paediatric Use

Refer to **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 (antabuse effect) 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

Compatibility with intravenous infusions and other drugs

Metronidazole infusion may be diluted to 1 in 5 or greater with appropriate volumes of Sodium Chloride 0.9%, Glucose-Saline combinations, Glucose 5% or Potassium Chloride injections 20 mmol/L and 40 mmol/L. While physically compatible with Compound Sodium Lactate Infusion (Hartmann's Solution) and Compound Sodium Chloride Infusion (Ringer's Solution), metronidazole is not chemically compatible with them over extended periods of time. Therefore, addition of metronidazole infusion to these solutions is not recommended. However, it may be delivered through the administration set Y-site of fast-running infusions of Hartmann's or Ringer's Solutions. While Glucose 10% is compatible with metronidazole infusion, its use as a diluent and vehicle is not recommended because of the high osmolarity of the resulting solution.

If dilution is necessary, the resultant solution should be held at 2°C to 8°C for no longer than 24 hours.

Refer to **Section 6.2 Incompatibilities** for product incompatibilities.

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 since it crosses the placenta and rapidly enters the fetal circulation rapidly. As it 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. In view of the drug's 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, drowsiness, dizziness, hallucinations, convulsions, or transient visual disorders and advised not to drive or operate 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 and 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. Proliferation of Candida may also occur in the vagina.

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 has 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.

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 hepatoxicity/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 effects

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 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, 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 Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Specific bactericidal activity against important obligate anaerobes and protozoa.

Mode 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 drug which include disruption of DNA and inhibition of nucleic acid synthesis.

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 drug 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*, *Balatidium 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.

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 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.

Bioavailability

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

Absorption

Following intravenous infusion, peak plasma levels of metronidazole occur at the end of the infusion. Traces are detected after 24 hours.

Distribution

Metronidazole is distributed widely throughout body tissues both intracellularly and extracellularly. 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

There is no significant plasma protein binding of metronidazole.

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-hydroxymethylmetronidazole, has some antiprotozoal activity in vitro.

Excretion

Approximately three-fourths of a single 750 mg oral dose is excreted as nitro-containing compounds (unchanged drug 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 drug due to the presence of water-soluble pigments which result from its metabolism.

Half Life

The biological half-life of a single intravenously administered dose of metronidazole has been determined as 7.3 hours ± 1.0 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

Water for injections, sodium chloride, dibasic sodium phosphate dodecahydrate and citric acid monohydrate.

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.

If dilution is necessary, the resultant solution should be held at 2°C to 8°C for no longer than 24 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not freeze. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Metronidazole Kabi 500 mg/100 mL is a colourless to pale yellow, ready to use solution.

Metronidazole Kabi 500 mg/100 mL (AUST R 310261) is supplied in 100 ml colourless glass bottle (type II glass) with halobutyl rubber stopper and cap or polyethylene bottle (KabiPac®) available in packs of 5, 10 or 12.

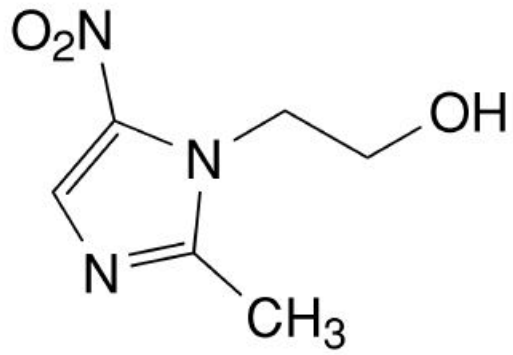
*Not all pack types and sizes may be marketed.

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-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethanol

Molecular Formula: C6H9N3O3

Molecular weight: 171.2

CAS no

443-48-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4- Prescription Only

8 SPONSOR

Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mount Kuring-gai NSW 2080
Australia
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9 DATE OF FIRST APPROVAL

21/11/2019

10 DATE OF REVISION

12 October 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6	Updated to include information on Candida infection and diarrhoea in breastfed infants.