

NEW ZEALAND DATA SHEET

Colpocin-T

1. PRODUCT NAME

Colpocin-T

Metronidazole Intravenous Infusion 500mg/100mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole is 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole B.P.

Each mL contains: metronidazole 5mg, citric acid monohydrate 0.81mg, dibasic sodium phosphate 1.5mg, sodium chloride 7.4mg. Each mL contains 3.4mg of sodium. The solution has a pH of between 4.5 and 6.0, for full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Colpocin-T infusion is an almost colourless to pale yellow isotonic, ready-to-use solution, requiring no dilution or buffering prior to administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Colpocin-T infusion is indicated:

- For treatment of anaerobic infections in patients for whom oral administration is not possible.
- When immediate anti-anaerobic therapy is required.
- 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 Infusion contains no microbial agent. It should be used in one patient on one occasion only and any residue discarded.

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

Adult:

Metronidazole should be infused intravenously at a rate of 5mL (25mg) per minute. Metronidazole infusion may be administered alone or concurrently (but separately) with other appropriate antibacterial agents in parenteral dosage forms (see Section **4.5 Compatibility with intravenous infusions and other medicines**). Other IV medicines or infusions should, if possible, be discontinued during its administration.

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 metronidazole dosage accordingly.

NEW ZEALAND DATA SHEET

Colpocin-T

Parenteral drugs should be inspected visually for particulate matter and discolouration prior to administration, wherever solution or container permit. 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.

Adults and children over 12 years

100mL containing 500mg Metronidazole B.P. by intravenous infusion every eight hours.

Children under 12 years

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

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.

With impaired hepatic function: 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.

With impaired renal function: In patients on twice weekly haemodialysis, metronidazole and its major active metabolite are rapidly removed during an 8 hour period of dialysis, so 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.

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

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

NEW ZEALAND DATA SHEET

Colpocin-T

NOTES:

Note: Prevention of infection at the surgical site requires that adequate tissue concentrations of the medicine 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 in children for some years, recent evidence concerning mutagenicity and tumorigenicity suggests caution be exercised when using the 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 Compatibility with Intravenous Infusions and Other Medicines**).

4.3 Contraindications

- Patients with evidence of a history of blood dyscrasias should not receive the medicine since occasionally leucopenia has been observed during its administration.
- Active organic disease of the central nervous system
- Hypersensitivity to metronidazole or other nitroimidazoles

4.4 Special warnings and precautions for use

Instructions to be given to patients:

- patients should be warned to refrain from consumption of alcohol whilst taking metronidazole
- patients should be advised to report any signs of toxicity, especially neurological disturbances, to the doctor
- patients should be warned about the possibility of their urine darkening in colour

Long term therapy: If metronidazole is to be administered for more than 10 days, it is recommended that haematological tests, especially total and differential leukocyte 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 drug should be discontinued immediately.

Cardiac function impairment: Care should be taken because of the sodium content in this dosage form.

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

Central nervous system: 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.

NEW ZEALAND DATA SHEET

Colpocin-T

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.

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

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, dizziness, hallucinations, convulsions or transient visual disorders.

Severe hepatic disease: Patients with severe hepatic disease metabolise metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously.

Interference with clinical, laboratory and other 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, ALT, 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.

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

Surgical drainage: Use of metronidazole does not obviate the need for aspiration of pus whenever indicated, such as in amoebic hepatic abscess or abscesses in other inaccessible positions.

Mutagenesis, tumorigenesis: Metronidazole has been found to be mutagenic in bacteria and some animal species. 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/risk ratio should therefore be carefully assessed in each case, particularly in relation to the severity of the disease and the age of the patient.

Carcinogenesis: 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 in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). The published results of one of the mouse studies indicated an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects were statistically significant.

NEW ZEALAND DATA SHEET

Colpocin-T

In the rat, there was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumours, among female rats administered metronidazole over that noted in the concurrent female control groups. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Results of a retrospective epidemiological study of 771 women treated with metronidazole for *T. vaginalis* have not revealed any statistically significant increase in cancer incidence over that expected in the normal population. The apparent increase in cervical carcinoma *in situ* in the metronidazole treated group was no different from the incidence in women documented to have had trichomoniasis not treated by metronidazole. Because of the limitations of a relatively small retrospective study, these results do not provide definite answers and the risk of carcinogenicity emphasises the need to avoid indiscriminate use of the medicine.

4.5 Interaction with other medicines and other forms of interaction

Alcohol: Metronidazole taken in combination with alcohol may produce abdominal cramps, nausea, vomiting, headaches and flushing. Patients should be advised not to take alcohol during therapy or for at least one day afterwards because of the possibility of a disulfiram-like reaction.

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 alcohol dependent patients who are receiving metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram in the previous two weeks.

Warfarin and other coumarin anticoagulants: Metronidazole has been reported to potentiate the anticoagulant effect of oral anticoagulants, resulting in prolongation of the prothrombin time. Concurrent administration should be avoided if possible. If metronidazole is used in patients receiving an oral anticoagulant, prothrombin time should be monitored and the dosage of the anticoagulant adjusted accordingly.

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

Phenobarbitone and phenytoin: The simultaneous administration of drugs that induce microsomal hepatic enzyme activity, such as phenobarbitone, pentobarbitone or 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.

Lithium: Initiation of short-term metronidazole therapy in patients stabilised on relatively high dosages 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 beginning metronidazole therapy to detect any increase that may precede clinical symptoms of lithium intoxication.

NEW ZEALAND DATA SHEET

Colpocin-T

Cimetidine: The simultaneous administration of drugs that decrease microsomal hepatic enzyme activity, such as cimetidine, may prolong the half-life and decrease the plasma clearance of metronidazole. It is not clear if ranitidine exerts a similar effect.

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 BCNU (Carmustine): Metronidazole should be used with caution in patients who are receiving BCNU or cyclophosphamide as a drug interaction shown in mice leads to increased toxicity.

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

Compatibility with intravenous infusions and other medicines

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 (Hartman'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 Hartman's or Ringer's Solutions. While Glucose 10% is compatible, its use as a diluent and vehicle is not recommended because of the high osmolarity of the resulting solution.

Metronidazole Infusion is incompatible with aluminium; do not use equipment containing aluminium components (e.g. needle or cannula hubs). Other drugs should not be added directly to Metronidazole Infusion.

4.6 Fertility, pregnancy and lactation

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. Although it has not been shown to be teratogenic in either human or animal studies, such a possibility cannot be excluded.

In addition, the drug has been shown to be tumorigenic in rodents as well as mutagenic *in vitro* and in some animal studies. It is therefore recommended that the drug's use for trichomoniasis in the 2nd and 3rd trimesters of pregnancy be restricted to those in whom local palliative treatment has been inadequate to control symptoms. In life threatening situations the benefit/risk ratio should be carefully considered.

There is some evidence that the fetal alcohol syndrome may be due to small quantities of acetaldehyde rather than alcohol. If this is the case then metronidazole should not be taken in association with alcohol by pregnant women. Metronidazole inhibits aldehyde dehydrogenase

NEW ZEALAND DATA SHEET

Colpocin-T

thereby permitting accumulation of acetaldehyde which is one of the breakdown products of ethanol.

Use in Lactation

Metronidazole is secreted in breast milk. In view of the tumorigenic and mutagenic potential of metronidazole, breast feeding is not recommended.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

More common reactions:

Dermatological: Rash.

Gastrointestinal: Nausea, anorexia, furry tongue, dry mouth, abdominal discomfort, glossitis, stomatitis (which may be associated with candida overgrowth - see **4.4 Special warnings and precautions for use**).

Nervous System: Metallic or unpleasant taste in the mouth, headaches.

Less common reactions:

Auditory and vestibular: Vertigo, tinnitus.

Biochemical abnormalities: Jaundice has been reported in one patient being treated for anaerobic infection.

Cardiovascular: Flattening of the T wave, prolongation of the QT interval, thrombophlebitis.

Dermatological: Mild erythematous eruption, pruritus, urticaria and flushing.

Gastrointestinal: Vomiting, diarrhoea, dyspepsia, constipation and oral mucositis have been reported. Patients with Crohn's disease are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported. There have been reports of cases of pseudomembranous colitis whilst on metronidazole therapy.

Genito-urinary: Darkening of urine (possibly due to metabolites). Dysuria, dryness of vagina or vulva, cystitis, a sense of pelvic pressure, very rarely dyspareunia, polyuria, incontinence, decrease in libido, proctitis and pyuria have been reported during metronidazole therapy (although all of these may be attributable to the underlying pathology).

Haematological and reticuloendothelial: Leucopenia (usually moderate and transient - see **4.4 Special warnings and precautions for use**). One case of bone marrow aplasia attributable to metronidazole has been reported. Rarely, reversible thrombocytopenia occurs. Very rare cases of agranulocytosis and neutropenia 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.

NEW ZEALAND DATA SHEET

Colpocin-T

Hypersensitivity: Stevens-Johnson Syndrome, fever, angioedema and rare anaphylactic shock have been reported.

Liver: Very rare cases of reversible abnormal liver function tests and cholestatic hepatitis have been reported.

Musculoskeletal: Joint pains, sometimes resembling serum sickness.

Nervous system: Lack of coordination, ataxia, convulsive seizures, confusion, irritability, dizziness, depression, weakness, insomnia, disorientation, syncope, dysarthria, encephalopathy, aseptic meningitis, peripheral neuropathy, characterised mainly by numbness or paraesthesia of an extremity (see **4.4 Special warnings and precautions for use**). Transient vision disorders such as diplopia and myopia have been reported.

Respiratory: Nasal congestion.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Clinical Features: Overdosage with metronidazole appears to be associated with very few abnormal signs or symptoms. Disorientation, ataxia, nausea and vomiting, peripheral neuropathy and seizures have been reported, especially after ingestion of large amounts.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mode of Action

Metronidazole is bactericidal, amoebicidal and trichomonocidal. The exact mode of action has not been fully elucidated. Metronidazole is reduced by low-redox-potential electron transfer proteins (eg. nitroreductases 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.

Microbiology

Metronidazole is active *in vitro* against anaerobic bacteria and as an antiprotozoal agent. It does not appear to possess any clinically relevant activity against facultative anaerobes or obligate aerobes. Against susceptible organisms, metronidazole is generally bactericidal at concentrations equal to or slightly higher than the minimal inhibitory concentrations (MIC).

Metronidazole has been shown to have *in vitro* activity against many anaerobic gram-negative bacilli including *Bacteroides fragilis* and other *Bacteroides* sp., *Fusobacterium*, *Eubacterium*, *Clostridium* and anaerobic *Streptococci*. 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 active ulcerative gingivitis.

Colpocin-T

Susceptibility tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. National Committee for Clinical Laboratory Standards). Standardised susceptibility test procedures require the use of laboratory control microorganisms 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 microorganism 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.

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.

NEW ZEALAND DATA SHEET

Colpocin-T

5.3 Preclinical safety data

Not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Citric acid monohydrate
- Dibasic sodium phosphate monohydrate
- Sodium chloride
- Water for injection

6.2 Incompatibilities

See section 4.5, **Compatibility with intravenous infusions and other medicines.**

6.3 Shelf life

Plastic Bag: 24 months from date of manufacture

Plastic Bottle: 36 months from date of manufacture

6.4 Special precautions for storage

Store at or below 25°C

6.5 Nature and contents of container

Bag: Plastic, polypropylene bag with type I rubber stopper, 100mL- 10 dose units.

Bottle: Plastic, polypropylene bottle, 100mL- 20 and 24 dose units.

Bottle: Plastic, polyethylene bottle, 100mL – 24 dose units.

6.6 Special precautions for disposal (and other handling)

See section 4.2 **Dosage and method of administration** for handling.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Multichem NZ Ltd

8 Apollo Drive, Rosedale 0632

Auckland, New Zealand

9. DATE OF FIRST APPROVAL

31/8/2006

10. DATE OF REVISION OF THE TEXT

15/4/2018

SUMMARY TABLE OF CHANGES

Date	Summary of Changes
20/4/2018	Updated datasheet to be in line with current source datasheet and updated to SPC format.
15/4/2019	Addition of a new pack size (20 PP bottle pack)