

DATA SHEET

1. METRONIDAZOLE-CLARIS (Metronidazole Intravenous Infusion 500 mg/100ml)

METRONIDAZOLE-CLARIS, Metronidazole Intravenous Infusion 500 mg/100ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METRONIDAZOLE-CLARIS 5 mg/ml

100 ml of solution for infusion containing 500 mg of Metronidazole For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

METRONIDAZOLE-CLARIS 5 mg/mL Infusion is a clear, colourless to pale yellow solution each mL contains metronidazole 5mg, together with sodium chloride, anhydrous disodium hydrogen phosphate, citric acid monohydrate and water for injections. The solution has a pH of between 4.5 and 6.0 with a calculated osmolarity of 310.8 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

METRONIDAZOLE-CLARIS 500mg/100ml Intravenous Infusion is indicated in adults and children when oral medication is not possible for the following indications:

- The prophylaxis of postoperative infections due to sensitive anaerobic bacteria particularly species of Bacteroides and anaerobic Streptococci, during abdominal, gynaecological gastrointestinal or colorectal surgery which carries a high risk of occurrence of this type of infection. The solution may also be used in combination with an antibiotic active against aerobic bacteria.
- The treatment of severe intraabdominal and gynaecological infections in which sensitive anaerobic bacteria particularly Bacteroides and anaerobic Streptococci have been identified or are suspected to be the cause.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Dose and method of administration

Method of Administration

METRONIDAZOLE-CLARIS 500mg/100ml Intravenous Infusion should be infused intravenously at an approximate rate of 5 ml/minute (or one bag infused over 20 to 60 minutes). Oral medication should be substituted as soon as feasible.

Prophylaxis against postoperative infections caused by anaerobic bacteria:

Primarily in the context of abdominal, (especially colorectal) and gynaecological surgery.

Antibiotic prophylaxis duration should be short, mostly limited to the post operative period (24

hours but never more than 48 hours). Various schedules are possible.

Adults: Intra-venous injection of single dose of 1000mg-1500mg, 30-60 minutes preoperatively or alternatively 500mg immediately before, during or after operation, then 500mg 8 hourly.

Children < 12 years: 20-30 mg/kg as a single dose given 1-2 hours before surgery. Newborns with a gestation age <40 weeks: 10 mg/kg body weight as a single dose before operation.

Anaerobic infections:

Intravenous route is to be used initially if patient symptoms preclude oral therapy. Various schedules are possible.

Adults: 1000mg – 1500mg daily as a single dose or alternatively 500mg every 8 hours. Children > 8 weeks to 12 years of age: The usual daily dose is 20-30mg/kg/day as a single dose or divided into 7.5 mg/kg every 8 hours. The daily dose may be increased to 40 mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days. Children < 8 weeks of age: 15 mg/kg as a single dose daily or divided into 7.5 mg/kg every 12 hours.

In newborns with a gestation age < 40 weeks, accumulation of metronidazole can occur during the first week of life, therefore the concentrations of metronidazole in serum should preferably be monitored after a few days of therapy.

Oral medication could be given, at the same dose regimen. Oral medication should be substituted as soon as feasible.

Duration of Treatment

Treatment for seven to ten days should be satisfactory for most patients but, depending upon clinical and bacteriological assessments, the physician 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 genital tract.

Bacterial vaginosis:

Adolescents: 400 mg twice daily for 5-7 days or 2000 mg as a single dose

Urogenital trichomoniasis

Adults and adolescents: 2000 mg as a single dose or 200 mg 3 times daily for 7 days or 400 mg twice daily for 5-7 days

Children < 10 years: 40 mg/kg orally as a single dose or 15 – 30 mg/kg/day divided in 2-3 doses for 7 days; not to exceed 2000 mg/dose

Giardiasis:

> 10 years: 2000 mg once daily for 3 days, or 400 mg three times daily for 5 days, or 500 mg twice daily for 7 to 10 days

Children 7 to 10 years: 1000 mg once daily for 3 days

Children 3 to 7 years: 600 to 800 mg once daily for 3 days Children 1 to 3 years: 500 mg once daily for 3 days

Alternatively, as expressed in mg per kg of body weight: 15-40 mg/kg/day divided in 2-3 doses.

Amoebiasis:

> 10 years: 400 to 800 mg 3 times daily for 5-10 days

Children 7 to 10 years: 200 to 400 mg 3 times daily for 5-10 days Children 3 to 7 years: 100 to 200 mg 4 times daily for 5-10 days

Children 1 to 3 years: 100 to 200 mg 3 times daily for 5-10 days

Alternatively, doses may be expressed by body weight 35 to 50 mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400 mg/day

Eradication of Helicobacter pylori in paediatric patients:

As a part of a combination therapy, 20 mg/kg/day not to exceed 500 mg twice daily for 7-14 days. Official guidelines should be consulted before initiating therapy

Elderly Population

Caution is advised in the elderly, particularly at high doses, although there is limited information available on modification of dosage.

Patients with renal failure

Routine adjustments of the dosage of Metronidazole are not considered necessary in the presence of renal failure.

No routine adjustment in the dosage of Metronidazole needs to be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD). However dosage reduction may be necessary when excessive concentrations of metabolites are found.

In patients undergoing haemodialysis, Metronidazole should be re-administered immediately after haemodialysis

Patients with advanced hepatic insufficiency

In patients with advanced hepatic insufficiency a dosage reduction with serum level monitoring is necessary.

4.3 Contraindications

- Patients with evidence of a history of blood dyscrasias should not receive metronidazole since occasionally leukopenia has been observed during its administration.
- Active organic disease of the central nervous system.
- Pregnancy (first trimester) - see Use In Pregnancy.
- Hypersensitivity to metronidazole.

4.4 Special warning and precautions

Long Term Therapy

For treatment over 10 days haematological tests are recommended. If abnormal neurological signs or leukopenia occurs metronidazole should be discontinued immediately.

Mutagenicity

Metronidazole has been found to be mutagenic in bacteria and some animal species. Reports of chromosomal aberrations have occurred after long periods and, in one incident, after 7 days treatment. While insufficient experimental evidence exists, the potential risk should be taken into account when prescribing metronidazole, especially in pregnancy.

Carcinogenicity

Tumorigenic activity has occurred in chronic oral administration of metronidazole in mice and rats, the most prominent being pulmonary lesions in the mouse.

All of the 5 mouse studies have shown this, including one study where the animals were dosed on an intermittent schedule (dosage during every 4th week only). One of the mouse studies indicated an increase in malignant lymphomas and pulmonary neoplasms associated with lifetime feeding of metronidazole.

Long term rat toxicity studies show a significant increase in various neoplasms, particularly mammary tumours. Two life-time tumorigenicity studies in hamsters have been reported to be negative.

Results of 771 women treated for *T. vaginalis* in a retrospective epidemiological study, failed to show any significant increase in cancer incidence. Risk of carcinogenicity emphasises the need to avoid indiscriminate use of metronidazole.

Animal Toxicity

The LD50 for dogs has been reported as 4.5g/kg. In mice and rats LD50 dosages have been reported in the range 1-5g/kg.

Cardiac Function Impairment

Care is required due to the sodium present (0.135 mmol/mL) in the injection.

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.

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 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 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.

Candidiasis

Candida overgrowth in the gastrointestinal or genital tract may occur during metronidazole therapy and may require treatment with an agent with activity against Candida.

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. The underlying mechanism and implications of this interaction are discussed under Use in Pregnancy.

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.

Warfarin: Metronidazole inhibits the breakdown of the more potent S-isomer of warfarin. This is the pharmacologically active metabolite of the racemic parent molecule. Therefore, the activity of warfarin is enhanced by metronidazole.

Phenobarbitone: Decreases the effect of metronidazole probably due to increased metabolism.

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.

Interference with Clinical Laboratory and Other Tests: Metronidazole may show negative interference with continuous flow spectrophotometry of aspartate aminotransferase (previously GOT) so that hepato-cellular damage which is detectable by raised serum AST may be missed.

NOTE: Caution should be exercised in patients receiving metronidazole I.V. and 40mmol potassium chloride injections concurrently as such combinations may be hypertonic.

4.6 Fertility, Pregnancy and Lactation

Category B2

Metronidazole should not be given in the first trimester of pregnancy as it crosses the placenta and enters foetal circulation rapidly. However, it has not been shown to be teratogenic in either human or animal studies.

It is recommended that the use for trichomoniasis in 2nd and 3rd trimester be restricted to those in whom local palliative treatment has been inadequate to control symptoms. In life threatening situations the risk/benefit ratio should be carefully considered.

Foetal alcohol syndrome, possibly due to acetaldehyde rather than alcohol, would prevent taking alcohol in association with metronidazole in pregnant women. Metronidazole inhibits aldehyde dehydrogenase, permitting accumulation of acetaldehyde (a breakdown product of ethanol).

Metronidazole is secreted in breast milk, the highest concentrations being 2 and 4 hours after administration, declining over the next 12 to 24 hours. Assuming tumorigenic and mutagenic potential of metronidazole, breastfeeding should be withheld for 12 to 24 hours after metronidazole administration thereby reducing the infant's exposure.

4.7 Effects on ability to drive and use machines

No studies have been performed following intravenous treatment with Metronidazole on the ability to drive and use machines. Therefore it is recommended that patients should not drive or use machines

4.8 Undesirable effects

Adverse Effects

More Common Reactions

Dermatological: Rash, pruritis, urticaria.

Gastrointestinal: Nausea, anorexia, furry tongue, dry mouth, abdominal discomfort, glossitis, stomatitis (which may be associated with Candida overgrowth - see Precautions).

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

Less Common Reactions

Auditory and Vestibular: Vertigo, tinnitus.

Biochemical Abnormalities: Jaundice has been reported in one patient being treated for anaerobic infection. Altered renal function tests were noted in 2 patients on combined metronidazole and tobramycin therapy for intra-abdominal sepsis.

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

Dermatological: Mild erythematous eruption.

Genito-Urinary: Darkening of urine (possibly due to a metabolite). Dysuria, dryness of vagina or vulva, cystitis, a sense of pelvic pressure, 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).

Musculoskeletal: Joint pains. *Respiratory:* Nasal congestion.

Serious or Life Threatening Reactions: Leukopenia is usually transient and disappears on withdrawal of the medicine. If paraesthesia occurs, the drug should be discontinued and the symptoms usually disappear.

Gastrointestinal: Vomiting, diarrhoea, dyspepsia in patients with anaerobic infections. *Cl. difficile colitis* (one case).

Haematological and Reticulo-Endothelial: Leukopenia (usually moderate and transient - see Warnings and Precautions). One case of bone marrow aplasia attributable to metronidazole has been reported.

Nervous System: Lack of co-ordination, ataxia, convulsive seizures, confusion, irritability, depression, weakness, insomnia, disorientation, peripheral neuropathy, characterised mainly by numbness or paraesthesia of an extremity (see Warnings).

4.9 Overdose

Symptoms

Overdosage with metronidazole appears to be associated with very few abnormal signs or symptoms. Disorientation and vomiting may occur, especially after ingestion of large amounts.

Treatment

Early gastric lavage is recommended, where metronidazole has been taken orally.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

Metronidazole, in common with tinidazole and nimorazole, is one of the nitroimidazole class of therapeutic agents and has activity against protozoa (*Trichomonas*, amoebae and *Giardia lamblia*) and anaerobic bacteria (including *Bacteroides*).

Metronidazole is reduced at the nitro group by intestinal bacteria, particularly anaerobes. A reactive intermediate is thereby formed which binds to critical sites in susceptible bacterial cells, with subsequent disruption of DNA and inhibition of its synthesis. Reduction is probably effected by low redox potential electron transport proteins which play a major role in the metabolism of anaerobes. The activity of metronidazole against *Trichomonas*, amoebae and *Giardia* is also likely to be attributable to disruption of existing DNA and inhibition of its synthesis in those organisms.

5.2 Pharmacokinetic properties

Absorption

Infusion: Peak plasma levels (mean of 18 mcg/mL) of metronidazole occur at the end of infusion of 500 mg over 20 minutes.

Distribution

Metronidazole is distributed widely through body tissues both intracellularly and extracellularly. It is found in saliva and breast milk in concentrations equivalent to those in serum. 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.

There is no significant plasma binding of metronidazole (less than 5%).

Metabolism and Excretion

Metronidazole is partly metabolised in the liver by both acid oxidation and glucuronic conjugation. Five metabolites of metronidazole have been identified in urine. These include the hydroxy metabolite (1-(2-hydroxyethyl)-2-hydroxy-methyl-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. About 15-20% 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 hydroxy-methyl analogue each account for about one third. The fate of the remainder of an administered dose is unknown.

Half-Life

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

Metronidazole is also excreted into saliva and breast milk reaching concentrations equivalent to those in plasma.

Antibiotic specific information*Anti-Microbial Spectrum:*

The MIC breakpoints separating susceptible from intermediately susceptible and intermediately susceptible from resistant organisms are as following:

$S \leq 4$ mg/l and $R > 4$ mg/l

The prevalence of acquired resistance may vary geographically and with time for selected species and local information is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether microorganisms will be susceptible to Metronidazole or not.

<i>Categories</i>
<u>SUSCEPTIBLE</u>
<i>Gram negative aerobes</i>
<i>Helicobacter pylori</i>
<i>Anaerobes</i>
<i>Bacteroides fragilis</i>
<i>Bifidobacterium</i> >> <i>resistant (70%)</i>
<i>Bilophila</i>
<i>Clostridium</i>
<i>Clostridium difficile</i>
<i>Clostridium perfringens</i>
<i>Eubacterium</i>
<i>Fusobacterium</i>
<i>Peptostreptococcus</i>
<i>Prevotella</i>
<i>Porphyromonas</i>
<i>Veillonella</i>
<u>RESISTANT</u>
<i>Gram positive aerobes</i>
<i>Actinomyces</i>
<i>Anaerobes</i>
<i>Mobiluncus</i>
<i>Propionibacterium acnes</i>
<u>ANTIPARASITICACTIVITY</u>
<i>Entamoeba histolytica</i>
<i>Giardia intestinalis</i>
<i>Trichomonas vaginalis</i>

Cross-resistance with tinidazole occurs.

6. PHARMACEUTICAL PARTICULARS

6.1 list of excipients

Sodium Chloride
Anhydrous Disodium Hydrogen Phosphate Citric Acid Monohydrate
Water for Injections

The total sodium content (derived from sodium chloride and anhydrous hydrogen phosphate) is 326.4 mg/100 mL per 500 mg of metronidazole. This must be considered in patients on a restricted sodium intake when calculating total daily sodium intake.

6.2 Incompatibilities

Metronidazole infusion may be diluted to 1 in 5 or greater with appropriate volumes of normal saline, dextrose-saline, dextrose 5% w/v and with 20mmol and 40mmol potassium chloride injections. Additives should not be introduced into metronidazole IV solution. If used with a primary intravenous fluid system, the primary solution should be discontinued during metronidazole infusion.

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.

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

6.3 Shelf life

36 months

6.4 Special precautions for storage

Protect from light. Store below 25°C.

Use within 7 days after removing infusion bag from the carton. Keep the infusion bag in the overwrap until time of use.

6.5 Nature and contents of container

Infusion Bags

- 1 x non-PVC Infusion Bags containing METRONIDAZOLE-CLARIS 500 mg in 100 mL (0.5% w/v)
- 5 x PVC and non-PVC Infusion Bags containing METRONIDAZOLE-CLARIS 500 mg in 100 mL (0.5% w/v)
- 6 x PVC Infusion Bags containing METRONIDAZOLE-CLARIS 500mg in 100mL (0.5% w/v)
- 10 x PVC and non-PVC Infusion Bags containing METRONIDAZOLE-CLARIS 500mg in 100mL (0.5% w/v)

Vials

- 1X100 ml vial containing METRONIDAZOLE-CLARIS 500 mg in 100 mL (0.5% w/v)
- 5X100 ml vial containing METRONIDAZOLE-CLARIS 500 mg in 100 mL (0.5% w/v)
- 10X100 ml vial containing METRONIDAZOLE-CLARIS 500 mg in 100 mL (0.5% w/v)

6.6 Special precautions for disposal

Use only if the solution is clear, without visible particles and if the container is undamaged.

Administer immediately following the insertion of infusion set.

Do not remove unit from overpouch until ready for use. The inner bag maintains the sterility of the product.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

The solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system. In patients maintained on intravenous fluids, METRONIDAZOLE-CLARIS 500mg/100ml Intravenous Infusion may be diluted with appropriate volumes of 0.9% sodium chloride solution, dextrose 5% - 0.9% sodium chloride solution, dextrose 5% w/v or potassium chloride infusions (20 and 40mmol/litre).

Using an incorrect administration technique might cause the appearance of fever reactions due to the possible introduction of pyrogens. In the case of adverse reaction, infusion must be stopped immediately.

The product should be used immediately after opening. Discard after single use.

Discard any unused portion.

Do not reconnect partially used bags.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

METRONIDAZOLE-CLARIS is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

9. DATE OF FIRST APPROVAL

30 of March 2006

10. DATE OF REVISION OF THE TEXT

14 March 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Sponsor details updated.
10	Date of revision, and footer date updated.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.