SUMMARY OF PRODUCT CHARACTERISTICS

FEST METRONIDAZOLE INFUSION 500MG/100ML

1 X 100ML

SUMMARY OF PRODUCT CHARACTERISTICS

METRONIDAZOLE INFUSION 0.5 G/100ML

1. Name of the medicinal product :

Generic Name: Metronidazole Infusion

2. Qualitative and Quantitative composition:

Each 100ml of solution for infusion contains 0.5g metronidazole.

Excipients:

Each ml of solution for infusion contains 8mg sodium chloride.

Each 100ml of solution for infusion contains 0.8g sodium chloride

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form:

Solution for infusion.

4. Clinical Particulars:

4.1 Therapeutic indications

Metronidazole 0.5g/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 Bacteriodes 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 Posology and method of administration

Method of Administration

Metronidazole 0.5g/100ml Intravenous Infusion should be infused intravenously at an approximate rate of 5 ml/minute (or one bottle 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

Known hypersensitivity to Metronidazole or other imidazole derivatives or any of the excipients (see 6.1 List of excipients).
Metronidazole is contraindicated in the first trimester of pregnancy.
Use of Metronidazole is contraindicated in patients with end stage liver damage, haematopoietic disorders and uncontrolled diseases of the central or peripheral nervous system.

4.4 Special warnings and precautions for use

Liver disease:

Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of Metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The risk/benefit ratio of using Metronidazole to treat trichomoniasis in such patients

should be carefully considered (for dosage adjustment see section 4.2). Plasma levels of Metronidazole should be closely monitored.

Active Central Nervous System disease:

Metronidazole should be used with caution in patients with active disease of the Central Nervous System. The treatment should be withdrawn in case of ataxia, dizziness, or confusion. The risk of aggravation of the neurological state should be considered in patients suffering from severe central and peripheral neurological diseases, fixed or progressive paraesthesia and epilepsy. Caution is required in patients with active disease of the central nervous system except for brain abscess.

Renal Disease:

Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.

Sodium restricted patients:

May be harmful to patients on a low sodium diet.

Alcohol:

Patients should be advised not to take alcohol during Metronidazole therapy and at least 48 hours afterwards because of a disulfram-like effect (flushing, vomiting, tachycardia). See Section 4.5.

Intensive or prolonged Metronidazole therapy:

As a rule, the usual duration of therapy with i.v Metronidazole or other imidazole derivatives is usually less than 10 days. This period may only be exceeded in individual cases after a very strict benefit-risk assessment. Only in the rarest possible case should the treatment be repeated. Limiting the duration of treatment is necessary because damage to human germ cells cannot be excluded.

Intensive or prolonged Metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction. If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible.

In case of prolonged treatment, occurrence of undesirable effects such as paraesthesia, ataxia, dizziness and convulsive crises should be checked. High dose regimes have been associated with transient epileptiform seizures.

Monitoring:

Regular clinical and laboratory monitoring (including leukocyte formula) are advised in cases of high-dose or prolonged treatment, in case of antecedents of blood dyscrasia, in case of severe infection and in severe hepatic insufficiency.

General:

Patients should be warned that Metronidazole may darken urine (due to Metronidazole metabolite).

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended concomitant therapy:

Alcohol: Disulfram-like effect (warmth, redness, vomiting, tachycardia).

Alcohol beverage and drugs containing alcohol should be avoided. Patients should be advised not to take alcohol during Metronidazole therapy and at least 48 hours afterwards because of a disulfram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).

Concomitant therapy requiring special precautions:

Oral anticoagulants (warfarin): increase of the effects of oral anticoagulants and the risk of haemorrhage (decrease in its liver catabolism). Prothrombin time should be monitored more frequently. The dose of oral anticoagulants should be adjusted during the treatment with Metronidazole and 8 days after withdrawal.

A large number of patients have been reported showing an increase in oral anticoagulant activity whilst receiving concomitant antibiotic therapy. The infectious and inflammatory status of the patient, together with their age and general well-being are all risk factors in this context. However, in these circumstances it is not clear as to the part played by the disease itself or its treatment in the occurrence of prothrombin time disorders. Some classes of antibiotics are more likely to result in this interaction, notably fluoroquinolones, macrolides, cyclines, cotrimoxazole and some cephalosporins.
Vecuronium (non depolarising curaremimetic): Metronidazole can potentialise the effects of vecuronium.
Combinations to be considered:
5 Fluoro-uracile: increase in the toxicity of 5 fluoro-uracile due to a decrease of its clearance.
Lithium: lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and Metronidazole. Lithium treatment should be tapered or withdrawn before administering Metronidazole. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive Metronidazole.
Barbiturates – Phenobarbital might induce the metabolism of Metronidazole, which could lead to decreased efficacy of Metronidazole.
Cholestyramine may delay or reduce the absorption of Metronidazole.
Concomitant administration of phenytoin and Metronidazole may affect the metabolism of Metronidazole.
Cimetidine inhibits the metabolism of Metronidazole.
Cyclosporine – Case reports indicate that concomitant treatment with Metronidazole and Cyclosporine might lead to increased serum levels of cyclosporine. Cyclosporine concentrations and creatinine levels should be monitored.
Busulfan: Plasma concentrations of busulfan may increase during concomitant treatment with metronidazole, which can result in serious busulfan toxicity.
Laboratory tests:
Metronidazole may immobilise Treponema and thus may lead to falsely positive Nelson's test.

4.6 Fertility, pregnancy and lactation

Clinical data on a large number of exposed pregnancies and animal data did not show a teratogenic or foetotoxic effect. However unrestricted administration of nitroimidazolene to the mother may be associated with a carcinogenic or mutagenic risk for the unborn or newborn child.
Therefore Metronidazole should not be given during pregnancy unless clearly necessary.
Metronidazole is contraindicated in the first trimester of pregnancy.
Metronidazole is excreted in breast milk. During lactation either breast-feeding or Metronidazole should be discontinued.

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

Common undesirable effects (>1/100 <1/10): gastrointestinal tract: diffuse symptoms of intolerance (like nausea, vomiting), metallic taste, stomatitis and glossitis and dry mouth; myalgia.
Uncommon undesirable effects (>1/1000, <1/100): leucopenia, headaches and

weakness.

Rare undesirable effects (>1/10,000, <1/1000):

General: fever, skin rashes, urticaria, erythema multiforme anaphylactic shock, Quincke oedema, pustolosis, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.

Neurology: drowsiness, dizziness, ataxia, peripheral neuropathy or transient epileptiform seizures, hallucinations, Encephalopathy, optic neuropathy and aseptic meningitis.

Blood: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia. Blood dyscrasia is generally reversible but fatal cases have been reported.

Liver: Abnormal function tests, cholestatic hepatitis jaundice, pancreatitis; rare and reversible cases of pancreatitis are reported.

Gastrointestinal: Mucositis, epigastralgia, nausea, vomiting, diarrhoea, anorexia.

Urine: darkening of urine.

Eyes: diplopia, myopia.

Herxheimer reaction

Changes in the blood picture as well as peripheral neuropathy observed after prolonged treatment or high dosages generally abate after treatment withdrawal.

Frequency, type and severity of adverse reactions in children are the same as in adults.

4.9 Overdose

Symptoms

In cases of overdose in adults, the clinical symptoms are usually limited to nausea, vomiting, ataxia and slight disorientation. In a preterm newborn, no clinical or biological sign of toxicity developed.

Treatment

There is no specific treatment for Metronidazole overdose, Metronidazole infusion should be discontinued. Patients should be treated symptomatically.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Metronidazole is an anti-infectious drug belonging to the pharmacotherapeutic group of nitroimidazole derivatives, which have effect mainly on strict anaerobes. This effect is probably caused by interaction with DNS and different metabolites.

Pharmacotherapeutic group: Antibacterials for systemic use: imidazole derivatives

ATC Code: J01XD01

and

Pharmacotherapeutic group: Antiprotozoals: nitroimidazole derivatives ATC Code: P01AB01.

Metronidazole has antibacterial and antiprotozoal actions and is effective against anaerobic bacteria and against Trichomonas vaginalis and other protozoa including Entamoeba histolytica and Giardia lamblia.

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.

Categories

SUSCEPTIBLE

Gram negative aerobes

Helicobacter pylori

Anaerobes

Bacteroides fragilis

Bifidobacterium>>resistant (70%)

Bilophila

Clostridium

Clostridium difficile

Clostridium perfringens

Eubacterium

Fusobacterium

Peptostreptococcus

Prevotella

Porphyromonas

Veillonella

RESISTANT

Gram positive aerobes

Actinomyces

Anaerobes

Mobiluncus

Propionibacterium acnes

ANTIPARASITIC ACTIVITY

Entamoeba histolytica

Giardia intestinalis

Trichomonas vaginalis

Cross–resistance with tindazol occurs.

5.2 Pharmacokinetic properties

Distribution: After administration of a single 500 mg dose, mean Metronidazole peak plasma concentrations of ca. 14 – 18 µg/ml are reached at the end of a 20 minute infusion. 2-hydroxy-metabolite peak plasma concentrations of ca. 3 µg/ml are obtained after a 1 g single i.v. dose. Steady state Metronidazole plasma concentrations of about 17 and 13 µg/ml are reached after administration of Metronidazole every 8 or 12 hours, respectively.

Plasma protein binding is less than 10%, and the volume of distribution 1.1 ±0.4 l/kg.

Metabolism: Metronidazole is metabolised in the liver by hydroxylation, oxidation and glucuronidation. The major metabolites are a 2-hydroxy- and an acetic acid metabolite.

Elimination: More than 50% of the administered dose is excreted in the urine, as unchanged Metronidazole (ca. 20% of the dose) and its metabolites. About 20% of the dose is excreted with faeces. Clearance is 1.3 ±0.3 ml/min/kg, while renal clearance is about 0.15 ml/min/kg. The plasma elimination half-life of Metronidazole is ca. 8 hours,

and of the 2-hydroxy-metabolite ca. 10 hours.
Special patient groups: The plasma elimination half-life of Metronidazole is not influenced by renal impairment, however this may be increased for 2-hydroxy- and an acetic acid metabolite. In the case of haemodialysis, Metronidazole is rapidly excreted and the plasma elimination half-life is decreased to ca. 2.5 h. Peritoneal dialysis does not appear to affect the elimination of Metronidazole or its metabolites.
In patients with impaired liver function, the metabolism of Metronidazole is expected to decrease, leading to an increase in the plasma elimination half-life. In patients with severe liver impairment, clearance may be decreased up to ca. 65%, resulting in an accumulation of Metronidazole in the body.

5.3 Preclinical safety data

Metronidazole has been shown to be non-mutagenic in mammalian cells *in vitro* and *in vivo*.
Metronidazole and a metabolite have been shown to be mutagenic is some tests with non mammalian cells.
Although Metronidazole has been shown to be carcinogenic in certain species of mice, it was not carcinogenic in either rats or guinea pigs. There is no suspicion of carcinogenicity in man.
Further preclinical data on repeated toxicity and toxicity to reproduction add no relevant knowledge for the prescriber.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Sodium chloride
Dilute hydrochloric acid
Water for Injections

6.2 Incompatibilities:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal product except for those mentioned in 6.6.

6.3 Shelf Life:

36 months

6.4 Special Precautions for storage:

Store in a cool, dry place. Protect from light.

6.5 Nature and contents of container:

Polypropylene (PP) infusion bottle sealed with PP combined cap (ring-pull type)
The bottle size is 100ml.
One bottle per baby carton.

6.6 Special precautions for disposal and other handling

Use only if the solution is clear, without visible particles and if the container is undamaged. Administer immediately following the insertion of infusion set.
The solution should be administered with sterile equipment using an aseptic technique.
The product should be used immediately after opening.
Discard after single use.

Discard any unused portion.

7. MARKETING AUTHORISATION HOLDER

Name: FEST PHARM. CO., LTD.

Address: 61, EMIR ROAD, SABON GARI, KANO, KANO STATE, NIGERIA

8. MARKETING AUTHORISATION NUMBER(S)

N.A.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

N.A.

1.3.2Labelling (outer & inner labels)

Please refer to labels on the specimens.

1.3.3 Package Insert (also known as patient information PIL)

Size: 128*214mm²

NAFDAC Reg. No.:

FEST METRONIDAZOLE INFUSION

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Metronidazole Infusion and other antibacterial drugs, Metronidazole Infusion should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNING

Metronidazole has been shown to be carcinogenic in mice and rats (see Precautions). Its use, therefore, should be reserved for the conditions described in the Indications and Usage section below.

DESCRIPTION

Metronidazole Infusion is a parenteral dosage form of the synthetic antibacterial agent 1-(2 - hydroxyethyl)-2-methyl-5-nitroimidazole.

Metronidazole Infusion is 100 mL single dose container, is a sterile, nonpyrogenic, isosmotic, buffered solution of 500 mg Metronidazole.

CLINICAL PHARMACOLOGY

Metronidazole is a synthetic antibacterial compound. Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms, with an average elimination half-life in healthy humans of eight hours.

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose), with renal excretion accounting for 6-15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation (1-(β-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid) and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 mL/min/1.73 m².

Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Both the parent compound and the metabolite possess in vitro bactericidal activity against most obligate anaerobic bacteria.

Metronidazole appears in cerebrospinal fluid, saliva and breast milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.

Plasma concentrations of metronidazole are proportional to the administered dose. An eight-hour intravenous infusion of 100-4,000 mg of metronidazole in normal subjects showed a linear relationship between dose and peak plasma concentration.

In patients treated with intravenous metronidazole, using a dosage regimen of 15 mg/kg loading dose followed six hours later by 7.5 mg/kg every six hours, peak steady-state plasma concentrations of metronidazole averaged 25 mcg/mL with trough (minimum) concentrations averaging 18 mcg/mL.

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function.

In one study, newborn infants appeared to demonstrate diminished capacity to eliminate metronidazole. The elimination half-life, measured during the first three days of life, was inversely related to gestational age. In infants whose gestational ages were between 28 and 40 weeks, the corresponding elimination half-lives ranged from 160 to 32.5 hours.

Microbiology

Metronidazole is active in vitro against most obligate anaerobes, but 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. Metronidazole has been shown to have in vitro and clinical activity against the following organisms:

Anaerobic gram-negative bacilli, including:

Bacteroides species, including the *Bacteroides fragilis* group (*B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*)

Fusobacterium species

Anaerobic gram-positive bacilli, including:

Clostridium species and susceptible strains of *Eubacterium*

Anaerobic gram-positive cocci, including:

Peptococcus species

Peptostreptococcus species

Susceptibility Tests

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to metronidazole; however, the rapid, routine susceptibility testing of individual isolates of anaerobic bacteria is not always practical, and therapy may be started while awaiting these results.

Quantitative methods give the most accurate estimates of susceptibility to antibacterial drugs. A standardized agar dilution method and a broth microdilution method are recommended.

Control strains are recommended for standardized susceptibility testing. Each time the test is performed, one or more of the following strains should be included: *Eubacterium lentum* ATCC 43055, *Bacteroides fragilis* ATCC 25285, and *Bacteroides thetaiotaomicron* ATCC 29741. The mode metronidazole MICs for these three strains are reported to be 0.125-0.25, and 0.5 mcg/mL, respectively.

A clinical laboratory test is considered under acceptable control if the results of the control strains are within one doubling dilution of the mode MICs reported for metronidazole.

A bacterial isolate may be considered susceptible if the MIC value for metronidazole is not more than 16 mcg/mL, for organism is considered resistant if the MIC is greater than 16 mcg/mL. A report of "resistant" from the laboratory indicates that the infecting organism is not likely to respond to therapy.

INDICATIONS AND USAGE

Treatment of Anaerobic Infections

Metronidazole Infusion is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with Metronidazole Infusion therapy. In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to Metronidazole Infusion.

Metronidazole Infusion is effective in *Bacteroides fragilis* infections resistant to clindamycin, chloramphenicol and penicillin.

Intra-Abdominal Infections, including peritonitis, intra-abdominal abscess and liver abscess caused by *Bacteroides* species including the *B. fragilis* group (*B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*), *Clostridium* species, *Eubacterium* species, *Peptococcus* species and *Peptostreptococcus* species.

Skin and Skin Structure Infections caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species and *Fusobacterium* species.

Gynecologic Infections, including endometritis, endomyometritis, tubo-ovarian abscess and postsurgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptostreptococcus* species and *Fusobacterium* species.

Bacterial Septicemia caused by *Bacteroides* species including the *B. fragilis* group and *Clostridium* species.

Bone and Joint Infections, as adjunctive therapy, caused by *Bacteroides* species including the *B. fragilis* group.

Central Nervous System (CNS)Infections, including meningitis and brain abscess, caused by *Bacteroides* species including the *B. fragilis* group.

Lower Respiratory Tract Infections, including pneumonia, empyema and lung abscess, caused by *Bacteroides* species including the *B. fragilis* group.

Endocarditis caused by *Bacteroides* species including the *B. fragilis* group.

Prophylaxis

The prophylactic administration of Metronidazole Infusion preoperatively, intraoperatively and postoperatively may reduce the incidence of postoperative infection in patients undergoing elective colorectal surgery which is classified as contaminated or potentially contaminated.

Prophylactic use of Metronidazole Infusion should be discontinued within 12 hours after surgery. If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism(s) so that appropriate therapy may be given (see Dosage and Administration).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Metronidazole Infusion and other antibacterial drugs, Metronidazole Infusion should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Metronidazole Infusion is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

WARNINGS

Convulsive Seizures and Peripheral Neuropathy

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesias of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

PRECAUTIONS

General

Patients with severe hepatic disease metabolize 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.

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

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with Metronidazole Infusion and requires treatment with a candidicidal agent.

Prescribing Metronidazole Infusion 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.

Laboratory Tests

Metronidazole is a nitroimidazole, and should be used with care in patients with evidence of or history of blood dyscrasias. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Tumorigenicity in Rodents - Metronidazole has shown evidence of carcinogenic activity in studies involving chronic, oral administration in mice and rats, but similar studies in the hamster gave negative results. Also, metronidazole has shown mutagenic activity in a number of in vitro assay systems, but studies in mammals (in vivo) tested to demonstrate a potential for genetic damage.

Pregnancy: Teratogenic Effects

Pregnancy Category B. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Reproduction studies have been performed in rats at doses up to five times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. Metronidazole administered intraperitoneally to pregnant mice at approximately the human dose caused fetotoxicity, administered orally to pregnant mice, no fetotoxicity was observed. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, these drugs should be used during pregnancy only if clearly needed.

Nursing Mothers

Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug for the mother. Metronidazole is excreted in breast milk in concentrations similar to those found in plasma.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Information For Patients

Patients should be counseled that antibacterial drugs including Metronidazole Infusion should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Metronidazole 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 taken exactly as directed. Skipping doses or not completing the full course of therapy 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 Infusion or other antibacterial drugs in the future.

ADVERSE REACTIONS

Two serious adverse reactions reported in patients treated with intravenous metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged oral administration of metronidazole, patients should be observed carefully if neurologic symptoms occur and a prompt evaluation made of the benefit/risk ratio of the continuation of therapy.

The following reactions have also been reported during treatment with Metronidazole Infusion:

Gastrointestinal: Nausea, vomiting, abdominal discomfort, diarrhea and an unpleasant metallic taste.

Hematopoietic: Reversible neutropenia (leukopenia).

Dermatologic: Erythematous rash and pruritus.

Central Nervous System: Headache, dizziness, syncope, ataxia and confusion.

Local Reactions: Thrombophlebitis after intravenous infusion. This reaction can be minimized or avoided by avoiding prolonged use of indwelling intravenous catheters.

Other: Fever. Instances of a darkened urine have also been reported, and this manifestation has been the subject of a 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 and seems to have no clinical significance.

The following adverse reactions have been reported during treatment with oral metronidazole:

Gastrointestinal: Nausea, sometimes accompanied by headache, anorexia and occasionally vomiting, diarrhea, epigastric distress, abdominal cramping and constipation.

Mouth: A short, unpleasant metallic taste is not unusual. Furry tongue, glossitis and stomatitis have occurred. These may be associated with a sudden overgrowth of *Candida* which may occur during effective therapy.

Hematopoietic: Reversible neutropenia (leukopenia), rarely, reversible thrombocytopenia.

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Central Nervous System: Convulsive seizures, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness and insomnia.

Hypersensitivity: Urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth or vaginal or vaginal yeast infection.

Renal: Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure and darkened urine.

Other: Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, pruritus and feeling of pelvic pulsion sometimes resembling "tension soreness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing or headache. A manifestation of the taste of alcoholic beverages has also been reported. Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported.

Crohn's disease patients are known to have an increased incidence of gastrointestinal and colorectal carcinomas. There have been some reports in the medical literature of breast and cervix 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. Crohn's disease is not an approved indication for Metronidazole Infusion.

OVERDOSAGE

Use of dosages of intravenous metronidazole higher than those recommended has been reported. These include the use of 27 mg/kg three times a day for 20 days, and the use of 70 mg/kg as a single loading dose followed by 7.5 mg/kg maintenance doses. No adverse reactions were reported in either of the two cases.

Single oral doses of metronidazole up to 15 g have been reported in suicide attempts and accidental overdoses. Symptoms reported included nausea, vomiting and ataxia.

Oral metronidazole has been studied as a radiation sensitizer in the treatment of malignant tumors. Neurotoxic effects, including seizures and peripheral neuropathy, have been reported after 5 to 7 days of doses of 6 to 10.4 g every other day.

Treatment: There is no specific antidote for overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION

In elderly patients the characteristics of metronidazole may be altered and therefore monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

Treatment of Anaerobic Infections

The recommended dosage schedule for adults is:

Loading Dose:	15 mg/kg infused over one hour (approximately 1 g for a 70 kg adult).
Maintenance Dose:	7.5 mg/kg infused over one hour every six hours (approximately 500 mg for a 70 kg adult). The first maintenance dose should be infused six hours following the initiation of the loading dose.

Parenteral therapy may be changed to oral metronidazole when conditions warrant, at the discretion of the physician and the response of the patient to Metronidazole Infusion therapy. The usual adult oral dosage is 7.5 mg/kg every six hours.

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

Patients with severe hepatic disease metabolize 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. Close monitoring of serum metronidazole levels and toxicity is recommended.

In patients receiving Metronidazole Infusion in whom gastric secretions are continuously removed by nasogastric aspiration, sufficient metronidazole may be removed in the aspirate to require reduction in serum levels.

The dose of Metronidazole Infusion should not be substantially reduced in anuric patients since accumulated metabolites may be rapidly removed by dialysis.

The usual duration of therapy is 7 to 14 days; however, infections of the bone and joint, respiratory tract and cardiovascular system may require longer treatment.

Prophylaxis

For surgical prophylactic use, to prevent postoperative infection in contaminated or potentially contaminated colorectal surgery, the recommended dosage schedule for adults is:

a. 15 mg/kg infused over 30 to 60 minutes and completed approximately one hour before surgery followed by

b. 7.5 mg/kg infused over 30 to 60 minutes at 6 and 12 hours after the initial dose.

It is important that (1) administration of the initial preoperative dose be completed approximately one hour before surgery so that adequate drug levels are present in the serum and tissues at the time of initial incision, and (2) Metronidazole Infusion be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of Metronidazole Infusion should be limited to the day of surgery only, following the above guidelines.

Caution: Metronidazole Infusion is to be administered by slow intravenous infusion only, either as a continuous or intermittent infusion. Additives should not be added to Metronidazole Infusion. If used with a primary intravenous fluid system, the primary fluid should be discontinued during metronidazole infusion. DO NOT USE SOLUTIONS CONTAINING ALUMINUM (e.g., NEEDLES, CANNULAE) THAT WOULD COME IN CONTACT WITH THE DRUG SOLUTION.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DRUG INTERACTIONS

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. This potentiation should be considered when Metronidazole Infusion is prescribed for patients receiving concomitant oral anticoagulation therapy.

The simultaneous administration of drugs that reduce microsomal liver enzyme activity (e.g., cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity (e.g., phenobarbital, may accelerate the elimination of metronidazole, resulting in decreased plasma levels. Impaired clearance of phenytoin has also been reported.

Alcoholic beverages should not be consumed during metronidazole therapy because a disulfiram-like reaction (abdominal cramps, nausea, vomiting, headaches and flushing may occur.

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have consumed alcohol within the last two weeks.

Drug/Laboratory Test Interactions

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides and hexokinase glucose. Values of zero may be obtained in any of the assays in which interference has been reported (routine enzymatic coupling of the reaction with oxidation-reduction of nicotinic adenine dinucleotide [NAD$^+$/NADH]). Interference is also possible in absorbance peaks of NADH (340nm) and metronidazole (320nm) at pH 7.

SPECIFICATION

100 ml, 0.5 g

STORAGE

Store in a dry place, below 30°C. Protect from light. Keep all medicines out of the reach of children

REFERENCES

1. M11-A3-Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard-Fifth Edition. National Committee for Clinical Laboratory Standards, and Subcommittee on Collaborative Evaluation of a Proposed Reference Dilution Method of Susceptibility Testing of Anaerobic Bacteria, Antimicrob. Agent Chemother. 14:456-557 (Oct.) 1978, and Tally, F.P., et al., Activity of Trovafloxacin, Antimicrob. Agents Chemother. 14:456-458 (Sept.) 1978.

2. Ralph, E.D. and Kirby, W.M.M., Bioassay of Metronidazole with Either Anaerobic or Aerobic Incubation. J. Infect. Dis. 132:587-591 (Nov.) 1975, or Goleb, et al., Determination of Metronidazole and its Major Metabolites in Biological Fluids by High Performance Liquid Chromatography, Br. J Clin. Pharmacol. 6:429-432, 1978.

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1.4 RegionalSummaries

1.4.1 Bioequivalence Trial Information Form (BTIF)

N.A.

1.4.2 Quality Information Summary (QIS)

Please refer to the attachment.

1.5 Electronic Review Documents

N.A.

1.6 Samples

Samples will be submitted later.