1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name: Metronidazole Intravenous Infusion BP (0.5 % w/v) - NIRMET

1.2 Strength: 0.5 %w/v

1.3 Pharmaceutical Dosage Form: Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative Composition:

Each100 ml contains
Metronidazole BP
Water for injection BP

Quantitative Composition:

Each 100 ml contains

Metronidazole BP	0.5 gm
Water for Injections BP	Q. S.

3. PHARMACEUTICAL FORM

Solution for Infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Metronidazole 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 Bacteriodes and anaerobic Streptococci have been identified or are suspected to be the cause.

4.2 Posology and Method of Administration:

Method of Administration

Metronidazole 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).

Prophylaxis against postoperative infections caused by anaerobic bacteria: Primarily in the context of abdominal, (especially colorectal) and gynecological 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:

Hypersensitivity to the active substance, to other imidazole derivatives or to any of the excipients No clinical studies have been conducted with Nirmin 10 plus solution in newborns, infants or children.

4.4 Special Warning and Precautions for use:

Liver disease:
Caution is needed in patients with severe hepatic impairment. The dose of metronidazole should be reduced as necessary. 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. Plasma levels of Metronidazole should be closely monitored.
Caution is needed in patients with hepatic encephalopathy. Patients with severe hepatic encephalopathy metabolize metronidazole slowly, with resultant accumulation of metronidazole. This may cause exacerbation of CNS adverse effects. The dose of metronidazole should be reduced as necessary.

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

Active Central Nervous System disease:
Metronidazole should be used with caution in patients with active disease of the Peripheral and Central Nervous System. Severe neurological disturbances (including seizures and peripheral and optic neuropathies) have been reported in patients treated with metronidazole. Stop metronidazole treatment if any abnormal neurologic symptoms occur such as ataxia, dizziness, confusion or any other CNS adverse reaction. The risk of aggravation of the neurological state should be considered in patients with fixed or progressive paraesthesia, epilepsy and active disease of the central nervous system except for brain abscess.
Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, dysarthria, and accompanied by CNS lesions seen on magnetic resonance imaging (MRI). CNS symptoms and CNS lesions, are generally reversible within days to weeks upon discontinuation of metronidazole.
Aseptic meningitis can occur with metronidazole. Symptoms can start within hours of dose administration and generally resolve after metronidazole therapy is discontinued.

Blood Dyscrasias
Metronidazole should be used with caution in patients with evidence or history of blood dyscrasia as agranulocytosis, leukopenia and neutropenia have been observed following metronidazole administration.

Renal Disease:
Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.Patients with renal impairment, including patients receiving

peritoneal dialysis, should be monitored for signs of toxicity due to the potential accumulation of toxic metronidazole metabolites.

Sodium restricted patients:
This medicinal product contains 13.5 mmol (310 mg) sodium per 100 mL. To be taken into consideration by patients on a controlled sodium diet.

Alcohol:
Patients should be advised to discontinue consumption of alcoholic beverages or alcohol-containing products before, during, and up to 72hours after taking metronidazole because of a disulfram-like effect (abdominal cramps, nausea, headaches, flushing, vomiting and tachycardia).

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:
Due to increased risk for adverse reactions, regular clinical and laboratory monitoring (including blood count) are advised in cases of high-dose, prolonged or repeated 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

4.5 Interaction with other Medicinal Products and other form of Interaction

Interaction related to the presence of sodium:
Disulfiram: Concurrent use of metronidazole and disulfiram may result in psychotic reactions and confusion. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.

Alcohol: Disulfiram-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 72 hours afterwards because of a disulfram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).

Concomitant therapy requiring special precautions: Oral anticoagulants (warfarin): metronidazole may increase the anticoagulant effects of warfarin and other oral anticoagulants, resulting in a prolongation of the prothrombin time and increased risk of haemorrhage (decrease in its liver catabolism). Patients taking metronidazole and warfarin or other oral coumarins concomitantly should have their prothrombin time and international normalized ratio (INR) monitored more frequently. Patients should be monitored for signs and symptoms of bleeding.

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. Cholestyramine may delay or reduce the absorption of Metronidazole. Phenytoin, barbiturates (phenobarbital): concomitant administration of drugs that induce microsomal liver enzyme activity, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole and therefore decrease its efficacy.

Cimetidine : concomitant administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may cause decreased metabolism and reduced plasma learance of metronidazole which may result in metronidazole toxicity.Concomitant use of metronidazole and CYP3A4 substrates (e.g., amiodarone, tacrolimus, cyclosporine,

carbamazepine, and quinidine) may increase respective CYP3A4-substrate plasma levels. Monitoring of plasma concentrations of CYP3A4 substrates may be necessary.

Busulfan: Plasma concentrations of busulfan may increase during concomitant treatment with metronidazole, which can result in serious busulfan toxicity such as sinusoidal obstruction syndrome, gastrointestinal mucositis, and hepatic veno-occlusive disease.

Laboratory tests: Metronidazole may immobilise Treponema and thus may lead to falsely positive Nelson's test. Metronidazole may interfere with serum aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase determinations. Metronidazole causes an increase in ultraviolet absorbance at 340 nm resulting in falsely decreased values.

4.6 Fertility, pregnancy and lactation

Pregnancy
Metronidazole crosses the placental barrier.
Clinical data on a large number of exposed pregnancies and animal data did not show a te ratogenic or foetotoxic effect. However unrestricted administration of nitroimidazolene to the mother may be associated with a carcinogenic or mutagenic risk for the unborn or ne wborn child.Therefore Metronidazole should not be given during pregnancy unless clearl y necessary.
Lactation
Metronidazole is excreted in breast milk. During lactation either breast-feeding or Metron idazole should be discontinued.
Fertility
There are no clinical data relating to the effect of metronidazole on fertility.Animal studie s demonstrated adverse effects on the male reproductive system that are wholly or partiall y reversible after treatment withdrawal

4.7 Side effects

Following are the undesirable effects of the Metronidazole:

- Nausea,
- Headache,
- Dry mouth,
- Abdominal distress
- Vomiting,
- Diarrhea
- Glossitis
- Stomatitis
- Vertigo
- Dizziness
- Ataxia

- Thrombophlebitis
- Very rarely convulsion

It shows disulfiram like effect

- Urticaria
- Pruritus

4.8 Undesirable effects

Not known when correctly administered.

Those that occur during overdose are usually reversible and regress when therapy is discontinued. Infusion via peripheral veins in general can cause irritation of the vein wall and thrombophlebitis.

4.9 Overdose

Symptoms

In cases of overdose in adults, the clinical symptoms are usually limited to nausea, vomiting and neurotoxic effects, including ataxia, slight disorientation, confusion, seizures and peripheral neurophathy.

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Pharmacotherpeutic Group : Antimicrobial – Antiprotozoal

ATC code: J 01 XD01

Metronidazole is a broad spectrum Antiprotozoal

Mode of Action:

The METRONIDAZOLE is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa. It has a broad spectrum of protozoal and antimicrobial activity. It shows antibacterial action against all anaerobic cocci, anaerobic grame –ve bacilli including bacteriodes species and anaerobic spore forming gram +VE bacilli. It is effective in infection due to entamoeba histolytic, giardia lambia, and trichomoniasis; it

shows selective toxicity to anaerobic microorganism. It also has a radio sensitizing effect on hypoxic tumor cells.
Its mechanism involves reduction by bacterial nitro reductase to an unstable intermediate, which interact with DNA. Effectively preventing further replication. A no. of factors affect the sensitivity of microorganism.

Mechanism of action:-

The Mechanism of action of Metronidazole is involves reduction by bacterial nitro reducates to an unstable intermediate, which interact with DNA and effectively preventing further replication. A no. of factors affects the sensitivity of micro-organism.

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 compared to patients with renal impairment.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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

Sodium Chloride BP
Disodium hydrogen phosphate BP
Citric acid Monohydrate BP
Water for injection BP

6.2 Shelf Life:

36 Months from the date of manufacture

6.3 Precaution for Storage:

Store below 30° C. Do not freeze. Protect from light.

6.4 Nature and Contents of Container:

Nirmet is available in 100ml plastic bottle with Nipple head cap.

7.0 Marketing Authorization Holder:

Aculife Healthcare Pvt. Ltd.
Village: Sachana
Taluka: Viramgam
District: Ahmedabad – 382150
Gujarat, India.

8.0 Marketing Authorization Number:

9.0 Date of first Authorization/Renewal of Authorization:

10.0 Date of last revision: ----