eurolife
healthcare pvt. Ltd.

Website : www.eurolifehealthcare.com
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CIN No : U51900MH1987PTC043106

Registered Office: Flat No. 105, Citi Apartment, Plot No. 21, Sector 16, Koparkhairane, Navi Mumbai-400 709, India.
Marketing Office: 69A, Mittal Chambers, Nariman Point, Mumbai-400 021, Maharashtra, India
Factories: **Unit-1**: Plot No. 520 Bhagwanpur, Roorkee-247 667, Uttarakhand, India
Unit-2: Plot No. 242, Bhagwanpur, Roorkee-247 667, Uttarakhand, India
Unit-3: Plot No. 69-72, SIDCO, Alathur-603 110 Tamilnadu, India
Unit-4: Tancsics Milihaly ut 15 szam, 2100, Godollo, Hungary

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

TONIMET (Metronidazole I.V. Infusion BP 500 mg/100 ml)

2. Qualitative and quantitative composition Each 100ml

contains:
Metronidazole BP …….500 mg
Sodium Chloride BP……..0.8 g
Water for Injections BP…….q.s.
For the full list of excipients, see Section 6.1.

3. Pharmaceutical form

Solution for Infusion.

A clear, almost colourless to pale yellow solution

4. Clinical particulars

4.1 Therapeutic indications

Metronidazole is indicated in adults and children for the treatment of severe infections due to anaerobic bacteria and for prophylaxis against such infections in patients for whom oral medication is not practical.

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 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

Known hypersensitivity to metronidazole.

4.4 Special warnings and precautions for use

Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction.
Reversible peripheral neuropathy has been reported with intensive or prolonged therapy with metronidazole.
If prolonged therapy is required the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible.
High dose regimens have been associated with transient epileptiform seizures.
Metronidazole should be administered with caution to patients with hepatic encephalopathy.
Metronidazole should be used with great care in patients with active disease of the central nervous system other than brain abscess.
Other imidazoles should be administered with caution to patients who have previously developed pancreatitis as an adverse reaction to metronidazole.
All patients receiving metronidazole for more than 10 days should be monitored, and treatment discontinued if signs of peripheral neuropathy or CNS toxicity develop
This solution contains sodium (as sodium chloride and disodium phosphate anhydrous), 15mmol (340mg) per 100ml dose, which needs to be taken into consideration by patients on a sodium-controlled diet.

4.5 Interaction with other medicinal products and other forms of interaction
Patients should not consume alcohol during and for at least 48 hours after metronidazole treatment because of a possible disulfiram-like (antabuse effect) reaction.
Metronidazole has been reported to enhance the anticoagulant effect of the warfarin and coumarin type anticoagulants, the dosage of which may therefore require reducing. Prothrombin times should be monitored. No interactions have been reported with the heparin-type anticoagulants.
Simultaneous treatment with lithium and metronidazole may impair clearance of lithium, accompanied by evidence of possible renal damage. Lithium treatment should be withdrawn or gradually reduced before administering metronidazole. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients treated with both lithium and metronidazole.
The rate of metabolism of metronidazole is increased in patients treated with pheno-barbitone, reducing metronidazole half-life to approximately 3 hours.
Metronidazole may impair the clearance of phenytoin.
Aspartate amino-transferase assays may give spuriously low values in patients treated with metronidazole, depending on the test method used.

Metronidazole has anti-treponemal activity and may mask the immunological response seen in untreated early syphilis; contacts of syphilis receiving metronidazole should probably be screened for an additional 4 - 8 weeks.
Metronidazole increases the toxicity of 5-fluorouracil by decreasing its renal clearance.
Metronidazole potentiates the activity of vecuronium.
Metronidazole may interact with disulfiram causing psychotic effects.

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 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.

Lactation

Metronidazole is excreted in breast milk. During lactation either breast-feeding or Metronidazole should be discontinued.

Fertility

There are no clinical data relating to the effect of metronidazole on fertility.
Animal studies demonstrated adverse effects on the male reproductive system that are wholly or partially reversible after treatment withdrawal

4.7 Effects on ability to drive and use machines

Patients should not drive or operate machinery if they become dizzy or drowsy.

4.8 Undesirable effects

There are no data available on adverse reactions from Baxter-sponsored clinical trials conducted with Metronidazole. The following adverse reactions have been reported with Metronidazole, listed by MedDRA System Organ Class (SOC), Preferred Term and frequency. The following frequency groupings are used: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).
Frequency, type and severity of adverse reactions in children are the same as in adults.

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
Blood and Lymphatic System Disorders	Leukopenia	uncommon
	Agranulocytosis	rare
	Pancytopenia	rare

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	Neutropenia Thrombocytopenia Eosinophilia	rare rare not known
Immune System Disorder	Anaphylactic shock Jarisch-Herxheimer reaction Hypersensitivity	rare rare not known
Metabolism and Nutrition Disorders	Decreased appetite	not known
Psychiatric Disorders	Hallucinations Depression Confusional state Insomnia	rare not known not known not known
Nervous System Disorders	Dysgeusia Headache Encephalopathy Meningitis aseptic Seizure Somnolence Neuropathy peripheral Ataxia DizzinessDysarthria Hypoaesthesia Paraesthesia	common uncommon rare rare rare rare rare rare rare not known not known not known
Eye Disorders	Optic neuropathy Diplopia Myopia	rare rare rare
Cardiac Disorders	Tachycardia Palpitations	not known not known
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	not known
Gastrointestinal Disorders	Glossitis Stomatitis Dry mouth Pancreatitis	common common common rare

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	Abdominal pain upper Diarrhoea Nausea Vomiting Constipation Tongue discoloration	rare rare rare rare not known not known
Hepatobiliary disorders	Jaundice cholestatic	rare
Skin and Subcutaneous Disorders	Stevens-Johnson syndrome Toxic epidermal necrolysis Angioedema Erythema multiforme Pruritus Swelling face Urticaria Hyperhidrosis Rash	rare rare rare rare not known not known not known not known not known
Musculoskeletal and Connective Tissue Disorders	Myalgia Muscle spasms Arthralgia	common not known not known
Renal and urinary disorders	Chromaturia Dysuria	rare not known
General and Administration Site Conditions	Asthenia Mucosal inflammation Pyrexia Injection site reaction Malaise Face oedema Oedema peripheral Chest pain Chills	uncommon rare rare not known not known not known not known not known not known
Investigations	Hepatic enzyme increased	not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

4.9 Overdose

There is no specific treatment for gross overdose of metronidazole. Metronidazole and its metabolites are efficiently removed during an 8 hour period of haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacodynamic properties:

Pharmacotherapeutic group: Antiprotozoals: nitroimidazole derivatives
ATC code: J01XD01

Metronidazole is an antimicrobial agent of the nitro-5-imidazole family. It is active against a wide range of pathogenic micro-organisms in particular species of Bacteroides, Clostridia, Eubacteria, Fusobacteria, Gardnerella vaginalis,and anaerobic cocci. It is also active against Balantidium coli, Entamoeba histolytica, Giardia lamblia and Trichomonas.
Metronidazole enters target cells of bacteria or protozoa probably by passive diffusion and is activated by reduction of the nitro group by pyruvate-ferredoxin oxidoreductase; the resultant unstable intermediate interacts with DNA effectively preventing replication

5.2 Pharmacokinetic properties

After injection, metronidazole is widely distributed in most body tissues and fluids reaching concentrations similar to those in plasma; it crosses the placenta and rapidly enters the foetal circulation. No more than 20% metronidazole is bound to plasma proteins. Peak steady state plasma concentrations of approximately 25µg/ml with a trough concentration of 18µg/ml have been reported in patients given an intravenous loading dose of 15mg/kg body weight followed by 7.5mg/kg every 6 hours.
Metronidazole is metabolised mainly by hepatic oxidation and glucuronide formation. At least half of the infused dose is recovered in urine after approximately 8 hours, as metronidazole but mainly as its principal metabolites: metabolite I (hydroxy form) present in plasma and urine and with 30 - 65% activity of metronidazole, and metabolite II (acid form) not detected in plasma but representing 40 - 50% of the substances in urine, with 5% activity of metronidazole. Metronidazole crosses the placenta and rapidly enters the foetal circulation. It is excreted in milk but the intake of a breastfed infant of a mother receiving the recommended dose would be considerably less than the therapeutic dose for infants.

The half-life of metronidazole is reported to be longer in neonates and in patients with liver disease; that of the hydroxyl metabolite is prolonged in patients with renal failure.
Metronidazole may impair the clearance of phenytoin.
Cimetidine has increased plasma concentrations of metronidazole and might increase the risk of neurological side-effects.

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.

Daily peroral metronidazole at 5-times the maximum human daily dose for greater than 4 weeks caused testicular toxicity and infertility in male rats. Fertility was restored in most subjects by 8 weeks after cessation of treatment, whereas the lower testicular and epididymal weights and sperm counts had improved but were still observed.

Daily peroral metronidazole at approximately 6-times the maximum human daily dose for ≥2 weeks caused testicular toxicity in male mice. Most indices of testicular toxicity were restored within 2 months after cessation of treatment, whereas the lower testicular and epididymal weights had improved but were still observed.

These studies demonstrate that the adverse effects of metronidazole on the male reproductive system are wholly or partially reversible after treatment withdrawal

6. Pharmaceutical particulars

6.1 List of excipients

Disodium phosphate dodecahydrate

Citric acid monohydrate

Sodium chloride

Water for Injections

6.2 Incompatibilities

Metronidazole solution must not be mixed with cefamandole nafate, cefoxitin sodium, 10%w/v dextrose infusion, compound sodium lactate infusion, penicillin G potassium.

Cefuroxime sodium is physically and chemically compatible with Metronidazole MacoPharma 0.5%w/v Solution for Infusion. The following drugs are physically compatible in terms of pH and appearance over the recommended period of administration, although chemical stability has not been demonstrated : amikacin sulphate, ampicillin sodium, carbenicillin sodium, cephazolin sodium, cefotaxime sodium, cephalothin sodium, chloramphenicol sodium succinate, clindamycin phosphate, gentamicin sulphate, hydrocortisone sodium succinate, latamoxef disodium, netilmicin sulphate and tobramycin sulphate.

In patients maintained on intravenous fluids, Metronidazole MacoPharma 0.5%w/v Solution for Infusion may be diluted with appropriate volumes of 0.9%w/v sodium chloride solution, isotonic dextrose and sodium chloride solution, 5%w/v dextrose, or 20 or 40mmol/litre potassium chloride solution

6.3 Shelf life

2 years

Use immediately on removal from overwrap.

6.4 Special precautions for storage

Store at temperature not exceeding 30 °C. Protect from light. Keep all medicines out of reach of children.

6.5 Nature and contents of container

The immediate container of the product is available in 100 ml L.D.P.E Bottles

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements. The product is for single use in one patient only. Discard any residue immediately after use. Do not use if container is damaged or if solution is not clear

7. Marketing authorization holder

EUROLIFE HEALTHCARE PVT. LTD.
UNIT-1, Khasra No- 520,
Bhagwanpur, Roorkee
Distt. Haridwar 247667 Uttarakhand (India)

8. Marketing authorisation number(s)

NA

9. Date of first authorisation/renewal of the authorisation

NA

10. Date of revision of the text

NA