TROZ™ 500mg/100mL Infusion

(Metronidazole)

ٹِروز ۵۰۰ ملی گرام/۱۰۰ ملی لیٹر انفیوژن

(میٹرونیڈازول)

WARNING:
Metronidazole has been shown to be carcinogenic. Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the indications and usage section below.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Troz 500mg/100mL Infusion
Each 100mL vial contains:
Metronidazole USP.....500mg
(Product Specs: USP)

PHARMACEUTICAL FORM
Solution for infusion

CLINICAL PARTICULARS
Therapeutic Indications
Troz 500mg/100mL Infusion is indicated in adults and children for the prophylaxis and treatment of infections which is caused by susceptible anaerobic micro-organisms.
The prevention of post-operative infections where anaerobic bacteria are expected to be causative pathogens

- The treatment of peritonitis, empyema, necrotizing pneumonia, osteomyelitis, puerperal sepsis, lung, liver and pelvic abscess, and post-operative wound infections.
- Skin and skin structure Infections
- Gynaecologic Infections including endometritis, endomyometritis, tubo-ovarian abscess, and post-surgical vaginal cuff infection.
- Bacterial septicemia
- Bone and Joint Infections, as adjunctive therapy.
- Central Nervous System (CNS) Infections, including meningitis and brain abscess,
- Endocarditis

Posology and method of administration
The dosage is adjusted according to the patient's individual response to therapy, her/his age and body weight and according to nature and severity of the disease.

Adults and Adolescents
Treatment of anaerobic infections
Troz 500mg/100mL Infusion is given as 500 mg (100 mL) every 8 hours. Alternatively, 1000 mg-1500 mg may be given daily as a single dose. In most cases a treatment course of 7 days will be sufficient.
If clinically indicated, treatment may be continued beyond this time although a duration of 10 days should not normally be exceeded.

Prophylaxis against post-operative infection caused by anaerobic bacteria:
Troz 500mg/100mL Infusion, with administration completed approximately one hour before surgery. The dose is repeated after 8 and 16 hours.
Elderly: Caution is advised in the elderly, at higher dose. Limited information available on modification of dosage.
Paediatric population
Treatment of anaerobic infections
Children > 8 weeks to 12 years of age: The usual daily dose is 20-30 mg/kg body weight per day as a single dose or divided into 7.5 mg per kg BW every 8 hours. The daily dose may be increased to 40 mg per kg BW, depending on the severity of the infection.

Neonates and infants < 8 weeks of age: 15 mg / kg body weight as a single dose daily or divided into 7.5 mg per kg BW every 12 hours.

In newborns with a gestational age < 40 weeks: Accumulation can occur during the first week of life; therefore, the concentrations in serum should preferably be monitored after a few days therapy.
Duration of treatment is usually 7 days. Serum concentration should preferably be monitored after a few days therapy.

Prophylaxis against postoperative infections caused by anaerobic bacteria
Children < 12 years: 20-30 mg/kg body weight 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 surgery.

Patients with renal insufficiency:
Limited data available. No routine dose adjustment is necessary in patients with renal failure undergoing intermittent peritoneal dialysis (IPD) or continuous ambulatory peritoneal dialysis (CAPD).

Patients with hepatic insufficiency:
Patients with severe liver disease will require lower doses. In patients with hepatic encephalopathy, the daily dosage should be reduced to one third and may be administered once daily.

Method of administration
For Intravenous use. The contents of one bottle are to be infused slowly

IV, i.e. 100mL max. over not less than 20 minutes, but normally over one hour.
Troz 500mg/100mL Infusion can also be diluted before administration, adding the medicinal product to an IV vehicle solution such as 0.9 % sodium chloride or 5 % glucose infusion solution.
Concurrently prescribed antibiotics are to be administered separately.

Contraindications
- Hypersensitivity to metronidazole or other nitroimidazole derivatives.

Special warnings and precautions for use
Patients with hepatic impairment
In patients with severe liver damage should only be used if its expected benefits clearly outweigh potential hazards.
Substantial impairment clearance may occur in the presence of advanced hepatic insufficiency.
Significant accumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. It should therefore be administered with caution to patients with hepatic encephalopathy.
Due to the risk of aggravation, it should also be used in patients with active or chronic severe peripheral and central nervous system diseases only if its expected benefits clearly outweigh potential hazards. Convulsive seizures, myoclonus and peripheral neuropathy, the latter mainly characterized by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurological signs demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

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

In the case of severe hypersensitivity reactions (e.g. anaphylactic shock), treatment must be discontinued immediately and established emergency treatment must be initiated by qualified healthcare professionals.

Severe persistent diarrhea occurring during treatment or during the subsequent weeks may be due to pseudomembranous colitis (in most cases caused by clostridium difficile). This intestinal disease, precipitated by the antibiotic treatment, may be life-threatening and requires immediate appropriate treatment. Anti-peristaltic medicinal products must not be given.

The duration of therapy should not exceed 10 days. Only in specific elective cases and if definitely needed, the treatment period may be extended, accompanied by appropriate clinical and laboratory monitoring.

Repeat therapy should be restricted as much as possible and to specific elective cases only. These restrictions must be observed strictly because the possibility of metronidazole developing mutagenic activity cannot be safely excluded.

Hepatotoxicity in patients with Cockayne Syndrome
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. It should not be used unless the benefit is considered to outweigh the risk and if no alternative treatment is available.
If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Prolonged therapy may be associated with bone marrow depression, leading to an impairment of hematopoiesis. Blood cell counts should be carefully monitored during prolonged therapy.

Special warnings / precautions regarding excipients
This medicinal product contains 335mg sodium.

Interference with laboratory tests.
It interferes with the enzymatic-spectrophotometric determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), triglycerides and glucose hexokinase resulting in decreased values (possibly down to zero).
Therefore, elevated liver enzyme concentrations may be masked when measured by continuous-flow methods based on endpoint decrease in reduced NADH. Unusually low liver enzyme concentrations, including zero values, have been reported. Patients should be warned that it may darken urine.

Interaction with other medicinal products and other forms of interaction
Interactions with other medicinal products

Amiodarone: QT interval prolongation and torsade de pointes have been reported with the co-administration of amiodarone. It may be appropriate to monitor QT interval on the ECG if amiodarone is used in combination with metronidazole.

Barbiturates: Phenobarbital may increase the hepatic metabolism, reducing its plasma half-life to 3 hours.

Busulfan: Co-administration may significantly increase the plasma concentrations of busulfan. The mechanism of interaction has not been described. Due to the potential for severe toxicity and mortality associated with elevated busulfan plasma levels, it should be avoided.

Carbamazepine: It may inhibit the metabolism of carbamazepine and raise the plasma concentrations as a consequence.

Cimetidine: Concurrently administered cimetidine may reduce the elimination in isolated cases and subsequently lead to increased its concentration in serum.

Contraceptive drugs: Some antibiotics can, in some exceptional cases, decrease the effect of contraceptive pills by interfering with the bacterial hydrolysis of steroid conjugates in the intestine and hereby reduce the re-absorption of unconjugated steroid. Therefore, the plasma levels of the active steroid decrease. This unusual interaction can occur in women with a high excretion of steroid conjugates through the bile. Oral contraceptive failure in association with different antibiotics, e.g. ampicillin, amoxicillin, tetracyclines and also in metronidazole is observed.

Coumarin derivatives: Concomitant treatment may potentiate the anticoagulant effect of these and increase the risk for bleeding as a consequence of decreased hepatic degradation. Dose adjustment of the anticoagulant can be necessary.

Ciclosporine: During simultaneous therapy with cyclosporine there is a risk for increased serum concentrations of cyclosporine. Frequent monitoring of cyclosporine and creatinine is required.

Disulfiram: Simultaneous administration of disulfiram may cause states of

confusion or even psychotic reactions. Combination of both agents must be avoided.

Fluorouracil: It inhibits the metabolism of concurrently administered fluorouracil, i.e. the plasma concentration of fluorouracil is increased.

Lithium: Caution is to be exercised when administered simultaneously with lithium salts, because raised serum concentrations of lithium have been observed. Lithium treatment should be tapered or withdrawn before administering. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Mycophenolat mofetil: Substances that alter the gastrointestinal flora (e.g., antibiotics) may reduce the oral bioavailability of mycophenolic acid products. Close clinical and laboratory monitoring for evidence of diminished immunosuppressive effect of mycophenolic acid is recommended during concomitant therapy with anti-infective agents.

Phenytoin: It inhibits the metabolism of concurrently administered phenytoin, i.e. the plasma concentration of phenytoin is increased. On the other hand, the efficacy is reduced when phenytoin is administered concurrently.

Tacrolimus: Co-administration may increase the blood concentrations of tacrolimus. Tacrolimus blood levels and renal function should be checked frequently and the dosage adjusted accordingly, particularly following initiation or discontinuation of therapy in patients who are stabilized on their tacrolimus regimen.

Other forms of interaction

Alcohol: Disulfiram-like effect. Alcoholic beverages and drugs containing alcohol should be avoided.

Fertility, Pregnancy and lactation

Fertility:
Indicate a potential negative influence of metronidazole on the male reproductive system if high doses lying well above the maximum recommended dose for humans were administered.
Pregnancy: It may also be used to treat infections if its expected benefits clearly outweigh any possible risk.
Lactation: It is secreted into breast milk, nursing should be stopped during therapy. Also after the end of the therapy, nursing should not be resumed before another 2-3 days because of the prolonged half-life.

Effects on ability to drive and use machines
Patients should be warned about the potential for drowsiness, dizziness, confusion, hallucinations, convulsions or transient visual disorders, and are advised not to drive or operate machinery if these symptoms occur.

Undesirable effects
Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

They are mainly associated with prolonged use or high doses. The most commonly observed effects include nausea, abnormal taste sensations and the risk of neuropathy in case of long term treatment.

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Granulocytopenia, agranulocytosis, pancytopenia and thrombocytopenia.	Very rare
	Leucopenia, aplastic anaemia	Not known
Immune system disorders	Severe acute systemic hypersensitivity reactions: anaphylaxis, up to anaphylactic shock.	Rare
	Angioedema.	Not known
Psychiatric disorders	Psychotic disorders, including states of confusion, hallucination	Very rare
	Depression	Not known
Nervous system disorders	Encephalopathy,headache,fever,drowsiness,dizziness, disturbancesin sight and movement,vertigo,ataxia, dysarthria,convulsions.	Very rare
	Somnolence or insomnia,myoclonuis,seizures,peripheral neuropathy manifesting as paraesthesia,pain,furry sensation, and tingling in the extremities. Aseptic meningitis.	Not known
Eye disorders	Disturbance of vision,e.g. diplopia,myopia.	Very rare
	Oculogyric crisis, optic neuropathy/neuritis (isolated cases)	Not known
Metabolism and nutrition disorders	Anorexia	Not known
Cardiac disorder	ECG changes like flattening of T wave	Rare
Infections and infestations	Superinfections with candida (e.g. genital infections)	Common
	Pseudomembranous colitis Details regarding emergency treatment.	Rare
Gastrointestinal disorders	Pancreatitis	Very rare
	Vomiting,nausea,diarrhoea,glossitis and stomatitis, eructation with bitter taste,epigastric pressure, metallic taste, furred tongue Dysphagia (caused by central nervous effects of metronidazole)	Not Known
Hepatobiliary disorders	Abnormal values of hepatic enzymes and bilirubin Hepatitis, jaundice	Very rare
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia	Very rare
Skin and subcutaneous tissue disorders	Allergic skin reactions, e.g. pruritus, urticaria, STEVENS JOHNSON syndrome, toxic epidermal necrolysis	Very rare
	Erythema multiforme	Not known
Renal and urinary disorders	Dark coloured urine (due to a metabolite of metronidazole)	Uncommon
General disorders and administration site conditions	Vein irritations (up to thrombophlebitis) after intravenous administration. States of weakness, fever	Not known

Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome

Overdose

There is no specific treatment or antidote that can be applied in the case of overdose of metronidazole. If required, it can be effectively eliminated by haemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmaco-therapeutic group: Anti-infectives for systemic use – imidazole derivatives
ATC Code: J01X D01

Mechanism of action
Metronidazole itself is ineffective. It is a stable compound able to penetrate into microorganisms. Under anaerobic conditions nitroso radicals acting on DNA are formed from metronidazole by the microbial

pyruvate ferredoxin-oxidoreductase, with oxidation of ferredoxin and flavodoxin. Nitroso radicals form adducts with base pairs of the DNA, thus leading to breaking of the DNA chain and consecutively to cell death.

PK/PD relationship

The efficacy of metronidazole mainly depends on the quotient of the maximum serum concentration (Cmax) and the minimum inhibitory concentration (MIC) relevant for the microorganism concerned.

Breakpoints

EUCAST breakpoints separating susceptible (S) from resistant organisms (R) are as follows:

Gram-positive anaerobes (S: ≤ 4 mg/l R > 4 mg/l) and Gram-negative anaerobes (S: ≤ 4 mg/l R > 4 mg/l).

Commonly susceptible species

Anaerobes: *Bacteroides fragilis, Clostridium difficile, Clostridium perfringens, Eubacterium, Fusobacterium spp, Peptoniphilus spp, Peptostreptococcus spp, Porphyromonas spp, Prevotella spp, Veillonella spp.*

Other micro-organisms: *Entamoeba histolytica, Gardnerella vaginalis, Giardia lamblia, Trichomonas vaginalis*, Inherently resistant organisms and all obligate aerobes.

Gram-positive micro-organisms: *Actinomyces spp, Enterococcus spp, Propionibacterium acnes, Staphylococcus spp, Streptococcus spp.*

Gram-negative micro-organisms: *Enterobacteriaceae, Haemophilus spp, Mobiluncus.*

Pharmacokinetic Properties

Absorption:

Metronidazole is readily absorbed from the gastrointestinal tract and the oral bioavailability is > 90%. Consequently, the same mg dose will result in similar exposure (AUC) when switching between intravenous and oral dosing.

Distribution

Metronidazole is widely distributed in body tissues after injection. It also diffuses across the placenta, and is found in breast milk of nursing mothers in concentrations equivalent to those in serum. Protein binding is less than 20 %, the apparent volume of distribution is 36 litres.

Biotransformation

Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. Its metabolites include an acid oxidation product, a hydroxy derivative and glucuronide. The major metabolite in the serum is the hydroxylated metabolite, the major metabolite in the urine is the acid metabolite.

Elimination

Approximately 80 % of the substance is excreted in urine with less than 10 % in the form of the unchanged drug substance. Small quantities are excreted via the liver. Elimination half-life is 8 (6-10) hours.

Characteristics in special patient groups:

The elimination half-life of metronidazole remains unchanged in the presence of renal failure; however, such patients retain the metabolites of metronidazole. The clinical significance of this is not known at present. Delayed plasma clearance and prolonged serum half-life (up to 30 h) is to be expected in severe liver disease.

PHARMACEUTICAL PROPERTIES

Incompatibilities: This medicinal product must not be mixed with other medicinal products.

Shelf life: 03 years

Special precautions for storage:

Protect from heat & sunlight, store at 25ºC. (Excursions permitted between 15ºC-25ºC)

Do not refrigerate or freeze.

The expiration date refers to the product correctly stored at the required condition.

Do not use if solution contains undissolved particles.

Keep out of the reach of children.

To be sold on the prescription of a registered medical practitioner only.

Presentation:

Troz 500mg/100mL Infusion is supplied in 100mL clear glass vial. Each 100mL contains: 500mg Metronidazole USP

REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER

Manufacturing site:

Bosch Pharmaceuticals (Pvt.) Ltd., Plot No. 209, Sector 23 Korangi Industrial area, Karachi Pakistan

Manufactured for:

Bosch Pharmaceuticals (Pvt.) Ltd., Plot No. 221-223, Sector 23 Korangi Industrial area, Karachi Pakistan

REGISTRATION / MARKETING AUTHORIZATION NUMBER

034856

DATE FROM WHICH MARKETING IS AUTHORIZED/RENEWAL OF AUTHORIZATION

08/12/2004 / 29/05/2019 Valid upto 07/12/2024

DATE OF REVISION OF THE TEXT

01/12/23

صرف وریدی استعمال کے لیے

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: دھوپ اور گرمی سے محفوظ ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔

ریفریجریٹر میں رکھنے یا منجمد ہونے سے بچائیں۔

محلول میں کوئی غیر حل پذیر ذرات نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف معتمد ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
Bosch Pharmaceuticals (Pvt.) Ltd.
209, Sector 23, Korangi Industrial Area,
Karachi - Pakistan.

For **Bosch Pharmaceuticals (Pvt.) Ltd.**
221-223, Sector 23, K.I.A. Karachi-Pakistan.