Bosch

For Medical Professional only

FLAZOL

500mg/100mL Infusion

(Metronidazole U.S.P.)

(Product Specs.: U.S.P.)

فلازول ۵۰۰ ملی گرام/۱۰۰ ملی لیٹر انفیوژن

(میٹرونیڈازول یو۔ایس۔پی)

DESCRIPTION

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

Metronidazole Injection, , in 100 mL is a sterile, nonpyrogenic, iso-osmotic, buffered solution of 500 mg Metronidazole, USP, 790 mg Sodium Chloride, USP, 47.6 mg Dibasic Sodium Phosphate Dried, USP and 22.9 mg Citric Acid Anhydrous, USP.

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 fecal excretion accounting for 6-15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(ß-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 strains of 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 109 to 22.5 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

INDICATIONS AND USAGE

Treatment of Anaerobic Infections

Metronidazole Injection, is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with Metronidazole Injection therapy. In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to Metronidazole Injection. Metronidazole Injection 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 Injection, 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 Injection, 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. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Metronidazole Injection, and other antibacterial drugs, Metronidazole Injection, 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 Injection, is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

WARNINGS

Central And Peripheral Nervous System Effects

Encephalopathy and peripheral neuropathy: Cases of encephalopathy and peripheral neuropathy (including optic neuropathy) have been reported with metronidazole.

Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, and dysarthria. CNS lesions seen on MRI have been described in reports of encephalopathy. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible.

Peripheral neuropathy, mainly of sensory type has been reported and is characterized by numbness or paresthesia of an extremity.

Convulsive seizures have been reported in patients treated with metronidazole.

Aseptic meningitis: Cases of aseptic meningitis have been reported with metronidazole. Symptoms can occur within hours of dose administration and generally resolve after metronidazole therapy is discontinued.

The appearance of abnormal neurologic signs and symptoms 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 Injection, to patients receiving corticosteroids or to patients predisposed to edema.

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

Prescribing Metronidazole Injection, 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 dyscrasia. 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.

Drug Interactions

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when Metronidazole Injection, is prescribed for patients on this type of anticoagulant therapy.

The simultaneous administration of drugs that induce microsomal liver enzyme activity, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

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

Alcoholic beverages should not be consumed during metronidazole therapy because 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 taken disulfiram 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 observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotine adenine dinucleotide (NAD+NADH). Interference is

due to the similarity in absorbance peaks of NADH (340nm) and metronidazole (322nm) at pH 7.

Carcinogenesis, Mutagenesis, and 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) failed 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 to the mother. Metronidazole is secreted 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 Injection, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Metronidazole Injection 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 Injection, or other antibacterial drugs in the future.

ADVERSE REACTIONS

The most serious adverse reactions reported in patients treated with metronidazole injection have been convulsive seizures, encephalopathy, aseptic meningitis, optic 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 Injection,

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

Hematopoietic: Reversible neutropenia (leukopenia).

Dermatologic: Erythematous rash and pruritus.

Central Nervous System: Encephalopathy, aseptic meningitis, optic neuropathy, headache, dizziness, syncope, ataxia, confusion and dysarthria.

Hypersensitivity: Urticaria, erythematous rash, Stevens-Johnson Syndrome, flushing, nasal congestion, dryness of the mouth (or vagina or vulva) and fever.

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 sharp, 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: Encephalopathy, aseptic meningitis, convulsive seizures, optic neuropathy, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, dysarthria, irritability, depression, weakness and insomnia.

Hypersensitivity: Urticaria, erythematous rash, Stevens-Johnson Syndrome, flushing, nasal congestion, dryness of the mouth (or vagina or vulva) and fever.

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

Other: Proliferation of Candida in the vagina, dyspareunia, decrease of libido, proctitis and fleeting joint pains sometimes resembling "serum sickness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing or headache. A modification 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 certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon 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 Injection.

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 75 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 dose 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 pharmacokinetics 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 instituted six hours following the initiation of the loading dose.

Parenteral therapy may be changed to oral metronidazole when conditions warrant, based upon the severity of the disease and the response of the patient to Metronidazole Injection treatment. 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 plasma metronidazole levels2 and toxicity is recommended.

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

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

The usual duration of therapy is 7 to 10 days; however, infections of the bone and joint, lower respiratory tract and endocardium 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:

1. 15 mg/kg infused over 30 to 60 minutes and completed approximately one hour before surgery; followed by
2. 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 Injection be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of Metronidazole Injection should be limited to the day of surgery only, following the above guidelines.

Caution: Metronidazole Injection is to be administered by slow intravenous drip infusion only, either as a continuous or intermittent infusion. Additives should not be introduced into Metronidazole Injection. If used with a primary intravenous fluid system, the primary solution should be discontinued during metronidazole infusion. DO NOT USE EQUIPMENT 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.

HOW SUPPLIED

Flazol Injection, is supplied in 100 mL single dose clear glass vial. Each 100mL vial contains: 500mg Metronidazole USP.

DIRECTION

Protect from heat & sunlight, store at 25ºC. (Excursions permitted between 15ºC-25ºC)Do not refrigerate or freeze.

Keep out of the reach of children.

Do not use if solution contains undissolved particle.

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

For suspected adverse drug reaction for BOSCH products, report at ade@bosch-pharma.com

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

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 مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

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