# Metronidazole Metrocor 5 mg/mL (0.5% w/v)

Solution for IV Infusion Antibacterial (Imidazole Derivative)

FORMULATION

PRODUCT DESCRIPTION
Pale yellow liquid filled in LDPE bottle

# CLINICAL PHARMACOLOGY

Metronidazole is an anti-infective 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

Pharmacotherapeutic group: Antibacterials for systemic use : Imidazole derivatives

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 metabolite

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-(b-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 approximately for inchiliff 1/31ii.

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 human 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

In patients treated with a 0.5% intravenous solution of 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 10.9 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 minima 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 species

Anaerobic gram-positive cocci, including:

## 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: Clostridium perfringens ATCC 13124, Bacteroides fragilis ATCC 25285, and Bacteroides thetaiotaemicron ATCC 29741. The mode Metronidazole MICs for those three strains are reported to be 0.25, 0.25 and 0.5 mca/mL respectively.

A clinical laboratory test is considered under acceptable control if the results of e control strains are within one doubling dilution of the mode MICs rep

A bacterial isolate may be considered susceptible if the MIC value for Metronidazole is not more than 16 mcg/mL. An 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. TREATMENT OF ANAEROBIC INFECTIONS

Metronidazole IV infusion is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with Metronidazole IV 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 IV infusion Metronidazole IV 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, Peptostreptococcus species, and Peptococcus niger. Skin and Skin Structure Infections caused by *Bacteroides species including the* B. fragilis group, Clostridium species, Peptococcus niger, Peptostrepto

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, Peptococcus niger, and Peptostreptococcus 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, empysema, and lung abscess, caused by Bacteroides species including the B. fragilis group. Endocarditis caused by Bacteroides species including the B. fragilis group.

### INDICATIONS

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

### DOSAGE AND ADMINISTRATION

the 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

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 IV infusion treatment.

The usual adult oral dosage is 7.5 mg/kg every six hours

Amaximum of 4g 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 

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 IV infusion should not be specifically reduced in anuric patients since accumulated metabolites may be rapidly remove dialysis The usual duration of the rapy is 7 to 10 days; however, infections of the bone and

ioint, lower respiratory tract, and endocardium may require longer treatmen

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

15 mg/kg infused over 30 to 60 minutes and completed approximately one hour before surgery, followed by: 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 pre-operative 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 IV infusion be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of Metronidazole IV infusion should be limited to the day of surgery only, following the above guidelines. Caution: Metronidazole IV infusion is to be administered by slow intravenous

drip infusion only, either as a continuous or intermittent infusion. IV admixtures containing Metronidazole and other drugs should be avoided. Additives should not be introduced into the Metronidazole IV infusion solution. 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, ETC.) THAT MAY CONTACT THE

DRUG SOLUTION.

Metronidazole IV infusion is a ready to use isotonic solution NO DILUTION OR BUFFERING IS REQUIRED.

Do not refrigerate.

Each container of Metronidazole IV infusion contains 13.5 mEg of sodium. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if cloudy or precipitated or if the seals are not intact.

Use sterile equipment. It is recommended that the intravenous administration ratus be replaced at least once every 24 hours

## CONTRAINDICATIONS

Metronidazole IV infusion is contraindicated in patients with a prior history of hypersensitivity to Metronidazole or other nitroimidazole derivat

# CONVULSIVE SEIZURES AND PERIPHERAL NEUROPATHY

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia 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

## General

Prescribing Metronidazole IV infusion in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provid-benefit to the patient and increases the risk of the development of drug-resistar

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 administered cautiously.

ministration of solutions containing sodium ions may result in sodium

retention. Care should be taken when administering Metronidazole IV 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 IV infusion and requires treatment with a candicidal agent.

Dosage Modification required in severe Renal Failure

Congestive Heart Failure

### Information for Patients

Patients should be counseled that antibacterial drugs including Metronidazole IV infusion should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Metronidazole IV 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 IV infusion or other antibacterial drugs in the future. Laboratory Test

Metronidazole is a nitroimidazole, and Metronidazole IV infusion should be used with caution in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during Metronidazole administration; however, no persistent hematologic abnormalities attributable to Metronidazole have been observed in clinical studies. Total and differential leukocyte counts are nended 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 IV infusion is prescribed for patients on this type of anticoagulant therapy, prothrombin time and INR should be carefully monitored.

The simultaneous administration of drugs that induce microsomal liver enzymes, 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

Describes the provided 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 nicotinamide adenine dinucleotide (NAD Image from Drug Label Content NADH). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and Metronidazole (322 nm) at pH 7.

## 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) failed to demonstrate a potential for genetic damage.

## PREGNANCY

Teratogenic Effects Pregnancy Category B

## 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 human milk in concentrations similar to those found in plasma. Unnecessary exposure of the infant to the drug should be avoided, and breastfeeding should generally be interrupted during treatment and for 1 to 2 days afterwards

## DEDIATRIC LISE

Safety and effectiveness in children have not been established.

## ADVERSE DRUG REACTIONS

The two most serious adverse reactions reported in patients treated with 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 prototinged data administration of Medicinizative, 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

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 LOCAL REACTIONS: Thrombophlebitis after intravenous infusion. This

reaction can be minimized or avoided by avoiding prolonged use of indwell OTHER: Fever, Instances of a darkened urine have also been reported, and this

manifestation has been the subject of a special investigation. Although the rigiment 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

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

MOUTH: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, 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

CARDIOVASCULAR: Flattening of the T-wave may be seen in

CENTRAL NERVOUS SYSTEM: Convulsive seizures, peripheral neuropathy,

HYPERSENSITIVITY: Urticaria, erythematous rash, flushing, nasal congestion,

dryness of mouth (or vagina or vulva), and fever. **RENAL:** Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure,

ond 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. Crohn's disease patients are known to have an increased incidence of astrointestinal and certain extraintestinal cancers. There have been some eports 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 IV infusion.

## OVERDOSE AND TREATMENT

Use of dosages of 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 madverse 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 include nausea, omiting, 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

# MANAGEMENT OF OVERDOSE

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

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

## STORAGE CONDITION

tore at temperatures not exceeding 30° C. Do not freeze. KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

## AVAII ARII ITY

LDPE Plastic Bottle x 100 mL (Box of 1's)

### DRP-4259 Date of First Authorization: March 08, 2013

Date of Revision of Package Insert: December 23, 2021



Manufactured for: UNOSOURCE PHARMA LTD. 503 / 504, 5th Floor, Hubtown Solaris, N.S. Phadke Marg, Andheri (East), Mumbai-400069, India

Imported and Distributed by:
AMBICA INTERNATIONAL CORPORATION No. 9 Amsterdam Extension, Merville Park Subd. Parañaque, Metro Manila