

**METRONIDAZOLE- metronidazole tablet, film coated**  
**PharmPak, Inc.**

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**Metronidazole Tablets USP**

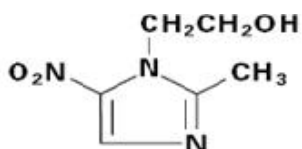
To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole tablets and other antibacterial drugs, metronidazole tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**WARNING**

Metronidazole has been shown to be carcinogenic in mice and rats (see **PRECAUTIONS**). Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the **INDICATIONS AND USAGE** section below.

**DESCRIPTION**

Metronidazole tablets, USP 250 mg or 500 mg is an oral formulation of the synthetic nitroimidazole antimicrobial, 2-methyl-5-nitro-1H-imidazole-1-ethanol, which has the following structural formula:



Metronidazole tablets USP contain 250 mg or 500 mg of metronidazole. Inactive ingredients include powdered cellulose, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hypromellose, polyethylene glycol, stearic acid, and titanium dioxide.

**CLINICAL PHARMACOLOGY**

**Absorption**

Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms. Following oral administration, metronidazole is well absorbed, with peak plasma concentrations occurring between one and two hours after administration.

Plasma concentrations of metronidazole are proportional to the administered dose. Oral administration of 250 mg, 500 mg, or 2,000 mg produced peak plasma concentrations of 6 mcg/mL, 12 mcg/mL, and 40 mcg/mL, respectively. Studies reveal no significant bioavailability differences between males and females; however, because of weight differences, the resulting plasma levels in males are generally lower.

**Distribution**

Metronidazole is the major component appearing in the plasma, with lesser quantities of metabolites also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. 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.

**Metabolism/Excretion**

The major route of elimination of metronidazole and its metabolites is via the urine (60% to 80% of the dose), with fecal excretion accounting for 6% to 15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(βhydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-ylacetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Both the parent compound and the hydroxyl metabolite possess *in vitro* antimicrobial activity.

Renal clearance of metronidazole is approximately 10 mL/min/1.73 m<sup>2</sup>. The average elimination half-life of metronidazole in healthy subjects is eight hours.

### **Renal Impairment**

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole.

Subjects with end-stage renal disease (ESRD; CLCR= 8.1±9.1 mL/min) and who received a single intravenous infusion of metronidazole 500 mg had no significant change in metronidazole pharmacokinetics but had 2-fold higher C<sub>max</sub> of hydroxy-metronidazole and 5-fold higher C<sub>max</sub> of metronidazole acetate, compared to healthy subjects with normal renal function (CLCR= 126±16 mL/min). Thus, on account of the potential accumulation of metronidazole metabolites in ESRD patients, monitoring for metronidazole associated adverse events is recommended (see **PRECAUTIONS**).

### **Effect of Dialysis**

Following a single intravenous infusion or oral dose of metronidazole 500 mg, the clearance of metronidazole was investigated in ESRD subjects undergoing hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A hemodialysis session lasting for 4 to 8 hours removed 40% to 65% of the administered metronidazole dose, depending on the type of dialyzer membrane used and the duration of the dialysis session. If the administration of metronidazole cannot be separated from the dialysis session, supplementation of metronidazole dose following hemodialysis should be considered (see **DOSAGE AND ADMINISTRATION**). A peritoneal dialysis session lasting for 7.5 hours removed approximately 10% of the administered metronidazole dose. No adjustment in metronidazole dose is needed in ESRD patients undergoing CAPD.

### **Hepatic Impairment**

Following a single intravenous infusion of 500 mg metronidazole, the mean AUC<sub>24</sub> of metronidazole was higher by 114% in patients with severe (Child-Pugh C) hepatic impairment, and by 54% and 53% in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to healthy control subjects. There were no significant changes in the AUC<sub>24</sub> of hydroxyl-metronidazole in these hepatically impaired patients. A reduction in metronidazole dosage by 50% is recommended in patients with severe (Child-Pugh C) hepatic impairment (see **DOSAGE AND ADMINISTRATION**). No dosage adjustment is needed for patients with mild to moderate hepatic impairment. Patients with mild to moderate hepatic impairment should be monitored for metronidazole associated adverse events (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

### **Geriatric Patients**

Following a single 500 mg oral or IV dose of metronidazole, subjects >70 years old with no apparent renal or hepatic dysfunction had a 40% to 80% higher mean AUC of hydroxy-metronidazole (active metabolite), with no apparent increase in the mean AUC of metronidazole (parent compound), compared to young healthy controls <40 years old. In geriatric patients, monitoring for metronidazole associated adverse events is recommended (see **PRECAUTIONS**).

### **Pediatric Patients**

In one study, newborn infants appeared to demonstrate diminished capacity to eliminate metronidazole. The elimination half-life, measured during the first 3 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**

#### **Mechanism of Action**

Metronidazole, a nitroimidazole, exerts antibacterial effects in an anaerobic environment against most obligate anaerobes. Once metronidazole enters the organism by passive diffusion and activated in the cytoplasm of susceptible anaerobic bacteria, it is reduced; this process includes intracellular electron transport proteins such as ferredoxin, transfer of an electron to the nitro group of the metronidazole, and formation of a short-lived nitroso free radical. Because of this alteration of the metronidazole molecule, a concentration gradient is created and maintained which promotes the drug's intracellular transport. The reduced form of metronidazole and free radicals can interact with DNA leading to inhibition of DNA synthesis and DNA degradation leading to death of the bacteria. The precise

mechanism of action of metronidazole is unclear.

### **Drug Resistance**

A potential for development of resistance exists against metronidazole.

Resistance may be due to multiple mechanisms that include decreased uptake of the drug, altered reduction efficiency, overexpression of the efflux pumps, inactivation of the drug, and/or increased DNA damage repair.

Metronidazole does not possess any clinically relevant activity against facultative anaerobes or obligate aerobes.

### **Activity In Vitro and in Clinical Infections**

Metronidazole has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

#### **Gram-positive anaerobes**

*Clostridium* species

*Eubacterium* species

*Peptococcus* species

*Peptostreptococcus* species

#### **Gram-negative anaerobes**

*Bacteroides fragilis* group ( *B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*)

*Fusobacterium* species

#### **Protozoal parasites**

*Entamoeba histolytica*

*Trichomonas vaginalis*

The following *in vitro* data are available, **but their clinical significance is unknown:**

Metronidazole exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 mcg/mL or less against most ( $\geq 90\%$ ) isolates of the following bacteria; however, the safety and effectiveness of metronidazole in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

#### **Gram-negative anaerobes**

*Bacteroides fragilis* group ( *B. caccae*, *B. uniformis*)

*Prevotella* species ( *P. bivia*, *P. buccae*, *P. disiens*)

#### **Susceptibility Tests:**

When available, the clinical microbiology laboratory should provide results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial or community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

#### **For Anaerobes:**

Quantitative methods are used to determine antimicrobial inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. For anaerobic bacteria, the susceptibility to metronidazole can be determined by the reference broth and/or agar method <sup>1,2</sup>.

The MIC values should be interpreted according to the criteria provided in the following Table

**Susceptibility Test Interpretive Criteria for Metronidazole against Anaerobes \*†**

MIC (mcg/mL)	Interpretation
$\leq 8$	Susceptible (S)
16	Intermediate (I)
$\geq 32$	Resistant (R)

\*Agar dilution method is recommended for all anaerobes

†Broth dilution method is recommended for testing of

*Bacteroides fragilis* group only; for this group, MIC values by agar and broth dilution methods are considered equivalent

A report of "Susceptible" (S) indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of "Intermediate" (I) implies that an infection due to the isolate may be appropriately treated in the body sites where the drugs are physiologically concentrated or when a high dosage of drug is used. A report of "Resistant" (R) indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentration usually achievable at the infection site; other therapy should be selected.

#### Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. <sup>1,2</sup>Standard metronidazole powder should provide a value within the MIC ranges noted in the following table:

Acceptable Quality Control Ranges for Metronidazole against Anaerobes

Quality Control Strain	Minimum Inhibitory Concentration (mcg/mL)	
	Agar	Broth
<i>Bacteroides fragilis</i> ATCC 25285	0.25–1.0	0.25-2.0
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	0.5–2.0	0.5-4.0
<i>Clostridium difficile</i> ATCC 700057	0.125-0.5	-
<i>Eggerthella lenta</i> ATCC 43055	-	0.125-0.5

#### **For protozoal parasites:**

Standardized tests do not exist for use in clinical microbiology laboratories.

#### **INDICATIONS AND USAGE**

**Symptomatic Trichomoniasis.** Metronidazole tablets are indicated for the treatment of *T. vaginalis* infection in females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures).

**Asymptomatic Trichomoniasis.** Metronidazole tablets are indicated in the treatment of asymptomatic *T. vaginalis* infection in females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. Since there is evidence that presence of the trichomonad can interfere with accurate assessment of abnormal cytological smears, additional smears should be performed after eradication of the parasite.

**Treatment of Asymptomatic Sexual Partners.** *T. vaginalis* infection is a venereal disease. Therefore, asymptomatic sexual partners of treated patients should be treated simultaneously if the organism has been found to be present, in order to prevent reinfection of the partner. The decision as to whether to treat an asymptomatic male partner who has a negative culture or one for whom no culture has been attempted is an individual one. In making this decision, it should be noted that there is evidence that a woman may become reinfected if her sexual partner is not treated. Also, since there can be considerable difficulty in isolating the organism from the asymptomatic male carrier, negative smears and cultures cannot be relied upon in this regard. In any event, the sexual partner should be treated with metronidazole tablets in cases of reinfection.

**Amebiasis** Metronidazole tablets are indicated in the treatment of acute intestinal amebiasis (amebic dysentery) and amebic liver abscess.

In amebic liver abscess, Metronidazole tablet therapy does not obviate the need for aspiration or drainage of pus.

**Anaerobic Bacterial Infections.** Metronidazole tablets are indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with metronidazole tablet therapy. In a mixed aerobic and anaerobic infection,

antimicrobials appropriate for the treatment of the aerobic infection should be used in addition to metronidazole tablets.

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, *Peptococcus* 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole tablets and other antibacterial drugs, metronidazole tablets 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

### Hypersensitivity

Metronidazole tablet are contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

In patients with trichomoniasis, metronidazole tablet are contraindicated during the first trimester of pregnancy (see **PRECAUTIONS**).

### Psychotic Reaction with Disulfiram

Use of oral metronidazole is associated with psychotic reactions in alcoholic patients who were using disulfiram concurrently. Do not administer metronidazole to patients who have taken disulfiram within the last two weeks (see **PRECAUTIONS, Drug Interactions**).

### Interaction with Alcohol

Use of oral metronidazole is associated with a disulfiram-like reaction to alcohol, including abdominal cramps, nausea, vomiting, headaches, and flushing. Discontinue consumption of alcohol or products containing propylene glycol during and for at least three days after therapy with metronidazole (see **PRECAUTIONS, Drug Interactions**).

## 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 (see **ADVERSE REACTIONS**).

### **Risk of Hepatotoxicity and Death 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 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. Obtain liver function tests prior to the start of therapy, within the first 2-3 days after initiation of therapy, frequently during therapy and after end of treatment. Discontinue metronidazole if elevation of liver function tests occurs, and monitor liver function tests until the baseline values are reached.

Advise patients with Cockayne syndrome to stop taking metronidazole immediately if they experience any symptoms of potential liver injury, such as abdominal pain, nausea, change in stool color or jaundice, and to contact their healthcare provider.

## **PRECAUTIONS**

### **General**

#### **Hepatic Impairment**

Patients with hepatic impairment metabolize metronidazole slowly, with resultant accumulation of metronidazole in the plasma. For patients with severe hepatic impairment (Child-Pugh C), a reduced dose of metronidazole is recommended. For patients with mild to moderate hepatic impairment, no dosage adjustment is needed but these patients should be monitored for metronidazole associated adverse events (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

#### **Renal Impairment**

Patients with end-stage renal disease may excrete metronidazole and metabolites slowly in the urine, resulting in significant accumulation of metronidazole metabolites. Monitoring for metronidazole associated adverse events is recommended (see **CLINICAL PHARMACOLOGY**).

#### **Fungal Superinfections**

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.

#### **Use in Patients with Blood Dyscrasias**

Metronidazole is a nitroimidazole and should be used with caution 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-Resistant Bacteria and Parasites**

Prescribing metronidazole in the absence of a proven or strongly suspected bacterial or parasitic infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria and parasites.

### **Information for Patients**

#### **Interaction with Alcohol**

Discontinue consumption of alcoholic beverages or products containing propylene glycol while taking metronidazole and for at least three days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur (see **CONTRAINDICATIONS and PRECAUTIONS, Drug Interactions**).

### **Treatment of Bacterial and Parasitic Infections**

Patients should be counseled that metronidazole should only be used to treat bacterial and parasitic infections. Metronidazole does not treat viral infections (*e.g.*, the common cold). When metronidazole 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 in the future.

### **Drug Interactions**

#### **Disulfiram**

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 (see **CONTRAINDICATIONS**).

#### **Alcoholic Beverages**

Abdominal cramps, nausea, vomiting, headaches, and flushing may occur if alcoholic beverages or products containing propylene glycol are consumed during or following metronidazole therapy (see **CONTRAINDICATIONS**).

#### **Warfarin and other Oral Anticoagulants**

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. When metronidazole is prescribed for patients on this type of anticoagulant therapy, prothrombin time and INR should be carefully monitored.

#### **Lithium**

In patients stabilized on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

#### **Busulfan**

Metronidazole has been reported to increase plasma concentrations of busulfan, which can result in an increased risk for serious busulfan toxicity. Metronidazole should not be administered concomitantly with busulfan unless the benefit outweighs the risk. If no therapeutic alternatives to metronidazole are available, and concomitant administration with busulfan is medically needed, frequent monitoring of busulfan plasma concentration should be performed and the busulfan dose should be adjusted accordingly.

#### **Drugs that Inhibit CYP450 Enzymes**

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.

#### **Drugs that Induce CYP450 Enzymes**

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.

#### **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 glucose hexokinase. 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<sup>+</sup>/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**

Tumors affecting the liver, lungs, mammary, and lymphatic tissues have been detected in several studies of metronidazole in rats and mice, but not hamsters.

Pulmonary tumors have been observed in all six reported studies in the mouse, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). Malignant liver tumors were increased in male mice treated at approximately 1500 mg/m<sup>2</sup> (similar to the maximum recommended daily dose, based on body surface area comparisons). Malignant lymphomas and pulmonary neoplasms were also increased with lifetime feeding of the drug to mice. Mammary and hepatic tumors were increased among female rats administered oral metronidazole compared to concurrent controls. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has shown mutagenic activity in *in vitro* assay systems including the Ames test. Studies in mammals *in vivo* have failed to demonstrate a potential for genetic damage.

Metronidazole failed to produce any adverse effects on fertility or testicular function in male rats at doses up to 400 mg/kg/day (similar to the maximum recommended clinical dose, based on body surface area comparisons) for 28 days. However, rats treated at the same dose for 6 weeks or longer were infertile and showed severe degeneration of the seminiferous epithelium in the testes as well as marked decreases in testicular spermatid counts and epididymal sperm counts. Fertility was restored in most rats after an eight week, drug-free recovery period.

### **Pregnancy:**

#### **Teratogenic Effects: Pregnancy Category B**

There are no adequate and well controlled studies of metronidazole in pregnant women. There are published data from case-control studies, cohort studies, and 2 meta-analyses that include more than 5000 pregnant women who used metronidazole during pregnancy. Many studies included first trimester exposures. One study showed an increased risk of cleft lip, with or without cleft palate, in infants exposed to metronidazole *in-utero*; however, these findings were not confirmed. In addition, more than ten randomized placebo-controlled clinical trials enrolled more than 5000 pregnant women to assess the use of antibiotic treatment (including metronidazole) for bacterial vaginosis on the incidence of preterm delivery. Most studies did not show an increased risk for congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy. Three studies conducted to assess the risk of infant cancer following metronidazole exposure during pregnancy did not show an increased risk; however, the ability of these studies to detect such a signal was limited.

Metronidazole crosses the placental barrier and its effects on the human fetal organogenesis are not known. Reproduction studies have been performed in rats, rabbits, and mice at doses similar to the maximum recommended human dose based on body surface area comparisons. There was no evidence of harm to the fetus due to metronidazole.

### **Nursing Mothers**

Metronidazole is present in human milk at concentrations similar to maternal serum levels, and infant serum levels can be close to or comparable to infant therapeutic levels. 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. Alternatively, a nursing mother may choose to pump and discard human milk for the duration of metronidazole therapy, and for 24 hours after therapy ends and feed her infant stored human milk or formula.

### **Geriatric Use**

In elderly geriatric patients, monitoring for metronidazole associated adverse events is recommended (see **CLINICAL PHARMACOLOGY, PRECAUTIONS**). Decreased liver function in geriatric patients can result in increased concentrations of metronidazole that may necessitate adjustment of metronidazole dosage (see **DOSAGE AND ADMINISTRATION**).

### **Pediatric Use**



Safety and effectiveness in pediatric patients have not been established, except for the treatment of amebiasis.

## ADVERSE REACTIONS

The following reactions have been reported during treatment with metronidazole:

**Central Nervous System:** The most serious adverse reactions reported in patients treated with metronidazole 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 administration of metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur. In addition, patients have reported headache, syncope, dizziness, vertigo, incoordination, ataxia, confusion, dysarthria, irritability, depression, weakness, and insomnia (see **WARNINGS**).

**Gastrointestinal:** The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and 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 therapy.

**Dermatologic:** Erythematous rash and pruritus.

**Hematopoietic:** Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

**Cardiovascular:** Flattening of the T-wave may be seen in electrocardiographic tracings.

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

**Renal:** Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately one patient in 100,000. 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.

**Other:** Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." Rare cases of pancreatitis, which generally abated on withdrawal of the drug, have been reported.

Patients with Crohn's disease 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 tablets.

## OVERDOSAGE

Single oral doses of metronidazole, up to 15 g, have been reported in suicide attempts and accidental overdoses. Symptoms reported include 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 of Overdosage:** There is no specific antidote for metronidazole overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

## DOSAGE AND ADMINISTRATION

### Trichomoniasis:

In the Female:

*One-day treatment* – two grams of metronidazole tablets, given either as a single dose or in two divided

doses of one gram each, given in the same day.

*Seven-day course of treatment* – 250 mg three times daily for seven consecutive days. There is some indication from controlled comparative studies that cure rates as determined by vaginal smears and signs and symptoms, may be higher after a seven-day course of treatment than after a one-day treatment regimen.

The dosage regimen should be individualized. Single-dose treatment can assure compliance, especially if administered under supervision, in those patients who cannot be relied on to continue the seven-day regimen. A seven-day course of treatment may minimize reinfection by protecting the patient long enough for the sexual contacts to obtain appropriate treatment. Further, some patients may tolerate one treatment regimen better than the other.

Pregnant patients should not be treated during the first trimester (see **CONTRAINDICATIONS**). In pregnant patients for whom alternative treatment has been inadequate, the one-day course of therapy should not be used, as it results in higher serum levels which can reach the fetal circulation (see **PRECAUTIONS, Pregnancy**).

When repeat courses of the drug are required, it is recommended that an interval of four to six weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before and after re-treatment.

In the Male: Treatment should be individualized as it is for the female.

### **Amebiasis**

Adults:

*For acute intestinal amebiasis (acute amebic dysentery):* 750 mg orally three times daily for 5 to 10 days.

*For amebic liver abscess:* 500 mg or 750 mg orally three times daily for 5 to 10 days.

*Pediatric patients:* 35 to 50 mg/kg/24 hours, divided into three doses, orally for 10 days.

### **Anaerobic Bacterial Infections**

In the treatment of most serious anaerobic infections, intravenous metronidazole is usually administered initially.

The usual adult oral dosage is 7.5 mg/kg every six hours (approx. 500 mg for a 70-kg adult). A maximum of 4 g should not be exceeded during a 24-hour period.

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.

### **Dosage Adjustments**

#### **Patients with Severe Hepatic Impairment**

For patients with severe hepatic impairment (Child-Pugh C), the dose of metronidazole tablets should be reduced by 50% (see **CLINICAL PHARMACOLOGY and PRECAUTIONS**).

#### **Patients Undergoing Hemodialysis:**

Hemodialysis removes significant amounts of metronidazole and its metabolites from systemic circulation. The clearance of metronidazole will depend on the type of dialysis membrane used, the duration of the dialysis session, and other factors. If the administration of metronidazole cannot be separated from the hemodialysis session, supplementation of metronidazole dosage following the hemodialysis session should be considered, depending on the patient's clinical situation (see **CLINICAL PHARMACOLOGY**).

### **HOW SUPPLIED**

#### **Metronidazole Tablets USP, 500 mg**

White colored, capsule shaped, film coated biconvex tablets with 'U' debossed on one side and '227' debossed on other side.

Bottles of 00: NDC 54348-740-00

Bottles of 04: NDC 54348-740-04

Bottles of 09: NDC 54348-740-09

Bottles of 14: NDC 54348-740-14

Bottles of 28: NDC 54348-740-28

**Storage and Stability:** Store at 20 °C to 25 °C (68 ° to 77 ° F) [see USP Controlled Room Temperature]. Protect from light.

**Please address medical inquiries to Unichem's toll free # 1-866-562-4616.**

## REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard -Eighth Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087 USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement*, CLSI document M100-S25. CLSI, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

## Rx only

Manufactured by:

**UNICHEM LABORATORIES LTD.**

Ind. Area, Meerut Road, Ghaziabad-201 003, India.

Manufactured for:





**UNICHEM**  
PHARMACEUTICALS (USA), INC.

Hasbrouck Heights, NJ 07604



06-R-04/2018

13010434

## Package Labeling: (54348-740-00)

NDC 54348-740-00 Store at 68-77 deg F PKGD by PHARMGAK SAN RAFAEL, CA 94901	PT: _____ Date: _____
METRONIDAZOLE TAB 500MG #1 UD Lot 12345 Exp. 6/18/20 12345 6/18/20	<b>METRONIDAZOLE TAB 500MG #1 UD</b> <b>MFG: UNICHEM</b>
GTIN 00354348740006 Serial BH00000010	For office use
 RX 0000441	 RX Only

Package Labeling: (54348-740-04)

PharmPak Label	
<p>NDC 54348-740-04 Store at 68-77 deg F</p> <p>PKGD by PHARMPAK SAN RAFAEL, CA 94901</p> <p>METRONIDAZOLE TAB 500MG #4</p> <p>Lot 12345 Exp. 6/18/20</p> <p>12345 6/18/20</p> <p>GTIN 00354348740044 Serial BH00000006</p>   <p>RX Only RX 0000442</p>	<p>PT: _____ Date: _____</p> <p><b>METRONIDAZOLE TAB 500MG #4</b> MFG: UNICHEM</p> <p>Take (4) tablets orally all at one time. Take with food or milk. Do not drink alcohol. Tome (4) tabletas al mismo tiempo. Tomela con comida o leche. No tome bebidas alcoholicas.</p>

Package Labeling: (54348-740-09)

<p>NDC 54348-740-09 Store at 68-77 deg F</p> <p>PKGD by PHARMPAK SAN RAFAEL, CA 94901</p> <p>METRONIDAZOLE TAB 500MG #9</p> <p>Lot 12345 Exp. 6/18/20</p> <p>12345 6/18/20</p> <p>GTIN 00354348740099 Serial BH00000002</p>   <p>RX Only RX 0000443</p>	<p>PT: _____ Date: _____</p> <p><b>METRONIDAZOLE TAB 500MG #9</b> MFG: UNICHEM</p> <p>Take ___ tablet(s) orally ___ times a day as directed. Take with food or milk. Finish medication. Do not drink alcohol. Tome ___ tableta(s) oralmente ___ veces al dia como es dirigido. Tomela con comida o leche. Termine medicina. No tome bebidas alcoholicas.</p>
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Package Labeling: (54348-740-14)

NDC 54348-740-14  
Store at 68-77 deg F

PKGD by PHARMPAK  
SAN RAFAEL, CA 94901

METRONIDAZOLE TAB  
500MG #14

Lot 12345  
Exp. 6/18/20

12345  
6/18/20

GTIN 00354348740143  
Serial BH00000137



RX Only

RX 0000444

PT: \_\_\_\_\_ Date: \_\_\_\_\_

**METRONIDAZOLE TAB 500MG #14**

**MFG: UNICHEM**

Take (1) tablet orally twice daily for 7 days. Take with food or milk. Finish medication. Do not drink alcohol. Tome (1) tableta 2 veces al dia por 7 dias. Tomela con comida o leche. Termine medicina. No tome bebidas alcoholicas.

**Package Labeling: (54348-740-28)**

NDC 54348-740-28  
Store at 68-77 deg F

PKGD by PHARMPAK  
SAN RAFAEL, CA 94901

METRONIDAZOLE TAB  
500MG #28

Lot 12345  
Exp. 6/18/20

12345  
6/18/20

GTIN 00354348740280  
Serial BH00000002



RX Only

RX 0000445

PT: \_\_\_\_\_ Date: \_\_\_\_\_

**METRONIDAZOLE TAB 500MG #28**

**MFG: UNICHEM**

Take (1) tablet orally twice daily for 14 days. Take with food or milk. Finish medication. Do not drink alcohol. Tome (1) tableta 2 veces al dia por 14 dias. Tomela con comida o leche. Termine medicina. No tome bebidas alcoholicas.

**METRONIDAZOLE**

metronidazole tablet, film coated

**Product Information**

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:54348-740(NDC:29300-227)
<b>Route of Administration</b>	ORAL		

**Active Ingredient/Active Moiety**

<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
METRONIDAZOLE (UNII: 140QMO216E) (METRONIDAZOLE - UNII:140QMO216E)	METRONIDAZOLE	500 mg

**Inactive Ingredients**

<b>Ingredient Name</b>	<b>Strength</b>
HYDROXYPROPYL CELLULOSE (90000 WAMW) (UNII: UKE75GEA7F)	
HYDROXYPROPYL CELLULOSE, LOW SUBSTITUTED (UNII: 2165RE0K14)	

<b>HYPROMELLOSE 2910 (5 MPAS)</b> (UNII: R75537T0T4)	
<b>POLYETHYLENE GLYCOL 400</b> (UNII: B697894SGQ)	
<b>POWDERED CELLULOSE</b> (UNII: SMD1X3XO9M)	
<b>STEARIC ACID</b> (UNII: 4ELV7Z65AP)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	

### Product Characteristics

<b>Color</b>	white	<b>Score</b>	no score
<b>Shape</b>	OVAL (capsule shaped)	<b>Size</b>	18mm
<b>Flavor</b>		<b>Imprint Code</b>	U;227
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54348-740-00	1 in 1 BOX	07/10/2019	
1		1 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:54348-740-04	1 in 1 BOX	07/10/2019	
2		4 in 1 BOTTLE; Type 0: Not a Combination Product		
3	NDC:54348-740-09	1 in 1 BOX	07/10/2019	
3		9 in 1 BOTTLE; Type 0: Not a Combination Product		
4	NDC:54348-740-14	1 in 1 BOX	07/10/2019	
4		14 in 1 BOTTLE; Type 0: Not a Combination Product		
5	NDC:54348-740-28	1 in 1 BOX	07/10/2019	
5		28 in 1 BOTTLE; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203458	07/10/2019	

**Labeler** - PharmPak, Inc. (175493840)

**Registrant** - PharmPak, Inc. (175493840)