

**METRONIDAZOLE- metronidazole tablet**  
**Rising Pharmaceuticals, Inc.**

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**METRONIDAZOLE Tablets, USP**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of METRONIDAZOLE, USP and other antibacterial drugs, METRONIDAZOLE, USP 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, USP 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, USP. Inactive ingredients include silicified microcrystalline cellulose, crospovidone, colloidal silicon dioxide and hydrogenated vegetable oil.

**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-( $\beta$ -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. 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;  $CL_{CR} = 8.1 \pm 9.1$  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  $C_{max}$  of hydroxy-metronidazole and 5-fold higher  $C_{max}$  of metronidazole acetate, compared to healthy subjects with normal renal function ( $CL_{CR} = 126 \pm 16$  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  $AUC_{24}$  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  $AUC_{24}$  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 exerts antibacterial effects in an anaerobic environment by the following possible mechanism: Once metronidazole enters the organism, the drug is reduced by intracellular electron transport proteins. Because of this alteration to the metronidazole molecule, a concentration gradient is created and maintained which promotes the drug's intracellular transport. Presumably, free radicals are formed which, in turn, react with cellular components resulting in death of the bacteria.

Metronidazole, USP is active against most obligate anaerobes, but does not possess any clinically relevant activity against facultative anaerobes or obligate aerobes.

### **Activity In Vitro and In Vivo**

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* minimum inhibitory concentrations (MIC's) of  $\leq 8$  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 Test Methods**

When available, the clinical microbiology laboratory should provide the 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 and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

**Anaerobic Techniques**

Quantitative methods are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. For anaerobic bacteria susceptibility to metronidazole can be determined by the reference broth or agar dilution method<sup>1,2</sup>. The MIC values obtained should be interpreted according to the following criteria:

**Susceptibility Test Interpretive Criteria for Metronidazole**

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

**For protozoal parasites:** Standardized tests do not exist for use in clinical microbiology laboratories.

A report of "Susceptible" 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" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of the drug product is physiologically concentrated or in situations where a high dosage of the drug product can be used.

This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations 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:

Agar and Broth Acceptable Quality Control Ranges for Metronidazole

Acceptable Quality Control Ranges for Metronidazole

QC 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

#### INDICATIONS AND USAGE

**Symptomatic Trichomoniasis.** METRONIDAZOLE, USP is 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, USP is 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, USP in cases of reinfection.

**Amebiasis.** METRONIDAZOLE, USP is indicated in the treatment of acute intestinal amebiasis (amebic dysentery) and amebic liver abscess.

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

**Anaerobic Bacterial Infections.** METRONIDAZOLE, USP is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with METRONIDAZOLE, USP therapy. In a mixed aerobic and anaerobic infection, antimicrobials appropriate for the treatment of the aerobic infection should be used in addition to METRONIDAZOLE, USP.

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, USP and other antibacterial drugs, METRONIDAZOLE, USP 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, USP is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

In patients with trichomoniasis, METRONIDAZOLE Tablets, USP is 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**).

## **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, USP 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, USP 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, USP 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, USP 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, USP should only be used to treat bacterial and parasitic infections. METRONIDAZOLE, USP does not treat viral infections (e.g., the common cold).

When METRONIDAZOLE, USP 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, USP 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, USP 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, USP 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, USP.

To report SUSPECTED ADVERSE REACTIONS, contact Rising Pharmaceuticals, Inc. at 1-866-562-4597 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## 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, USP, 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, USP 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 250 mg are white to off-white, round shaped tablets debossed with "MCR 104" on one side and plain on other side and supplied as bottles of 100's, 250's, 500's counts.

NDC Number	Size
64980-235-01	100's count Bottle
64980-235-25	250's count Bottle
64980-235-05	500's count Bottle

METRONIDAZOLE Tablets, USP 500 mg are white to off-white, oval shaped tablets debossed with "MCR 105" on one side and plain on other side and supplied as bottles of 50's, 100's, 500's counts.

NDC Number	Size
64980-236-50	50's count Bottle
64980-236-01	100's count Bottle
64980-236-05	500's count Bottle

**Storage and Stability:** Store below 77°F (25°C) and protect from light.

## 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-third Informational Supplement*, CLSI document M100-S23. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.

## Rx only

Manufactured for:  
Rising Pharmaceuticals, Inc.  
Allendale, NJ 07401

Manufactured by:  
Appco Pharma LLC  
Somerset, New Jersey 08873

Revised Dec 2015

—————**PRINCIPAL DISPLAY PANEL 250mg**—————

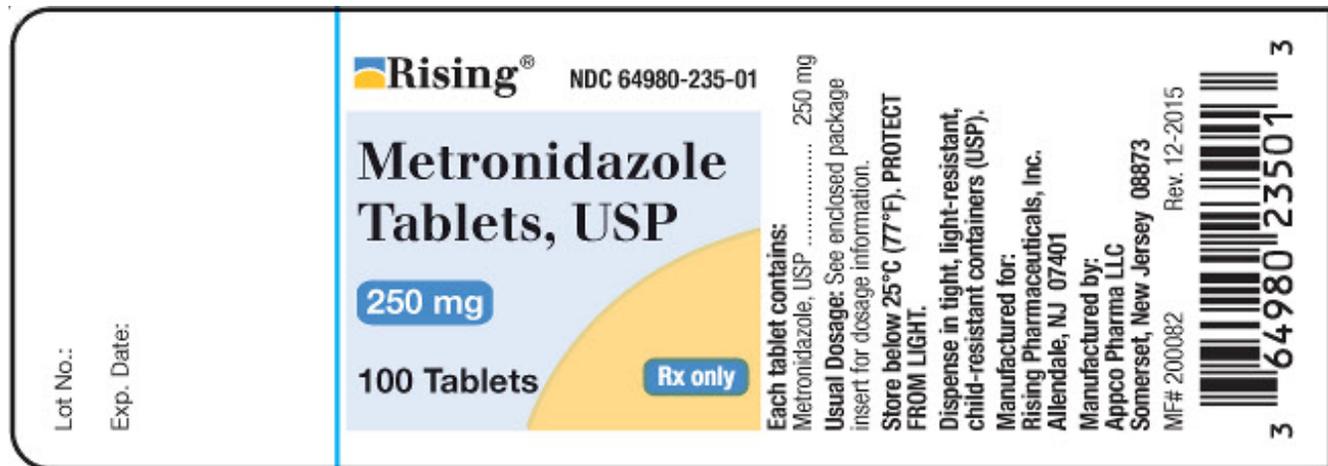
**Rising®** NDC 64980-235-01

**Metronidazole  
Tablets, USP**

250 mg

100 Tablets

Rx Only



PRINCIPAL DISPLAY PANEL 500mg

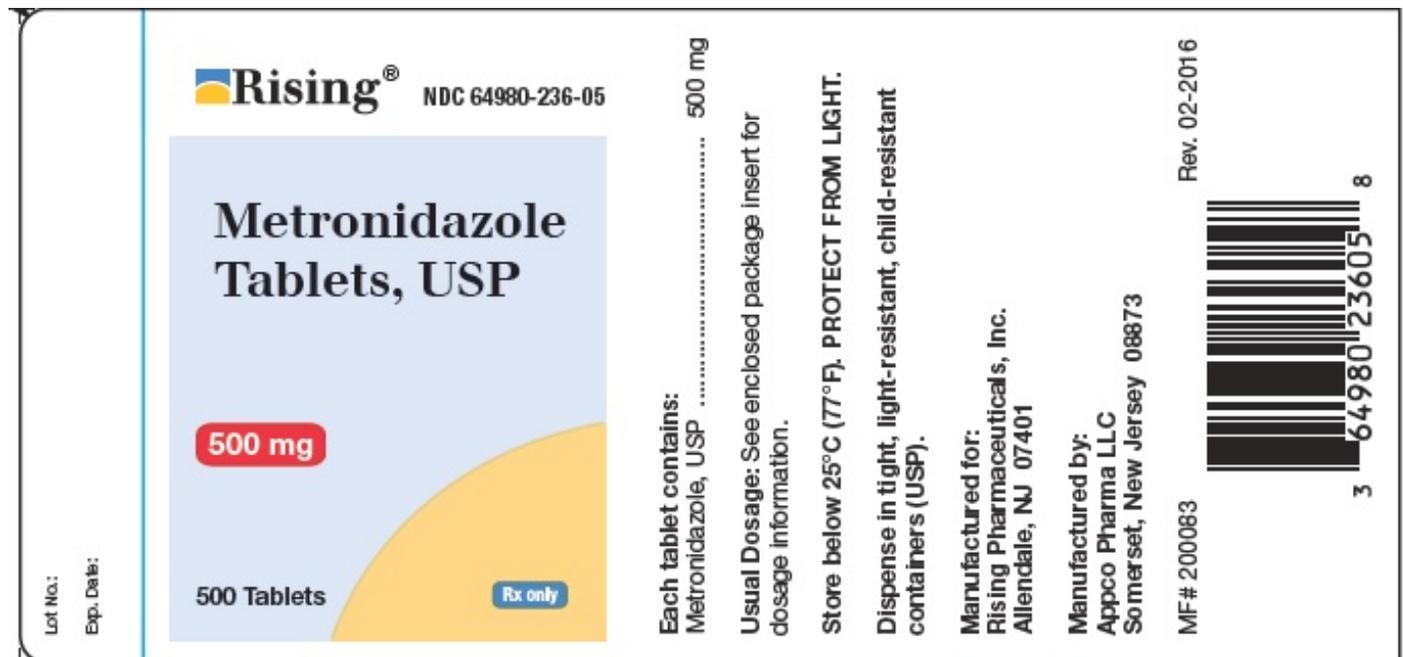
Rising® NDC 64980-236-05

Metronidazole Tablets, USP

500 mg

500 Tablets

Rx Only



METRONIDAZOLE

metronidazole tablet

Product Information

Product Type

HUMAN PRESCRIPTION DRUG

Item Code (Source)

NDC:64980-235

Route of Administration ORAL

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METRONIDAZOLE (UNII: 140QMO216E) (METRONIDAZOLE - UNII:140QMO216E)	METRONIDAZOLE	250 mg

### Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSPVIDONE (UNII: 2S7830E561)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYDROGENATED COTTONSEED OIL (UNII: Z82Y2C65EA)	

### Product Characteristics

Color	white (white to off-white)	Score	no score
Shape	ROUND	Size	9mm
Flavor		Imprint Code	MCR;104
Contains			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64980-235-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/2016	
2	NDC:64980-235-25	250 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/2016	
3	NDC:64980-235-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/2016	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205245	02/22/2016	

## METRONIDAZOLE

metronidazole tablet

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:64980-236
Route of Administration	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METRONIDAZOLE (UNII: 140QMO216E) (METRONIDAZOLE - UNII:140QMO216E)	METRONIDAZOLE	500 mg

## Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSPVIDONE (UNII: 2S7830E561)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYDROGENATED COTTONSEED OIL (UNII: Z82Y2C65EA)	

## Product Characteristics

Color	white (white to off-white)	Score	no score
Shape	ROUND	Size	9 mm
Flavor		Imprint Code	MCR;105
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64980-236-50	50 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/2016	
2	NDC:64980-236-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/2016	
3	NDC:64980-236-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/2016	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205245	02/22/2016	

**Labeler** - Rising Pharmaceuticals, Inc. (041241766)

## Establishment

Name	Address	ID/FEI	Business Operations
APPCO PHARMA LLC		078510186	manufacture(64980-235, 64980-236)

Revised: 12/2017

Rising Pharmaceuticals, Inc.