FLAGYL®
(metronidazole) extended-release tablets, 750 mg

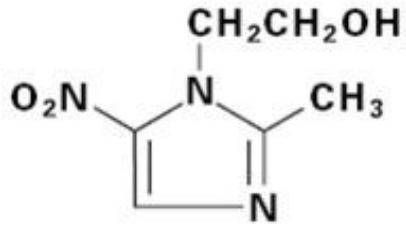
To reduce the development of drug-resistant bacteria and maintain the effectiveness of FLAGYL ER®, and other antibacterial drugs, FLAGYL ER® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

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 conditions described in the **INDICATIONS AND USAGE** section below.

DESCRIPTION

FLAGYL metronidazole extended-release tablets is an oral formulation of the synthetic nitroimidazole antimicrobial agent, 2-methyl-5-nitro-1*H*-imidazole-1-ethanol, which has the following structural formula:



FLAGYL (metronidazole) extended-release tablets, 750 mg (indicated below as FLAGYL ER) contain 750 mg of metronidazole USP. Inactive ingredients include hypromellose, lactose, magnesium stearate, polyethylene glycol, poly (meth) acrylic acid ester copolymers, polysorbate 80, silicon dioxide, simethicone emulsion, talc, titanium dioxide, FD&C Blue No. 2 Aluminum Lake.

CLINICAL PHARMACOLOGY

Absorption

Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms.

FLAGYL ER 750 mg tablets contain 750 mg of metronidazole in an extended-release formulation which allows for once-daily dosing. The steady state pharmacokinetics were determined in 24 healthy adult female subjects with a mean ± SD age of 28.8 ± 8.8 years (range: 19–46).[2] The pharmacokinetic parameters of metronidazole after administration of FLAGYL ER 750 mg under fed and fasting conditions are summarized in the following table.

Steady State Pharmacokinetic Parameters of Metronidazole after 750 mg of FLAGYL ER Given Once a Day for 7 Days

	FLAGYL ER 750 mg daily Mean±SD (N=24)	
Parameter	**fed**	**fasted**
$AUC_{(0-24)}$ (µg•hr/mL)	211±60.0	198±75.3
C_{max} (µg/mL)	19.4±4.7	12.5±4.8
C_{min} (µg/mL)	3.4±2.0	4.2±2.2
T_{max} (hrs)	4.6±2.4	6.8±2.8
$T_{½}$ (hrs)	7.4±1.6	8.7±2.2

Relative to the fasting state, the rate of metronidazole absorption from the extended-release tablet is increased in the fed state resulting in alteration of the extended-release characteristics.

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-(ß-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. 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^2.[1] 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±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 Cmax of hydroxy-metronidazole and 5-fold higher Cmax of metronidazole acetate, compared to healthy subjects with

normal renal function (CL_{CR}=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_{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. FLAGYL ER tablets should not be administered to patients with severe (Child-Pugh C) hepatic impairment unless it is deemed that the benefits outweigh the risks in these patients. No dosage adjustment is needed for patients with mild to moderate hepatic impairment. Patients with hepatic impairment who receive the usual recommended dose of FLAGYL ER tablet 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 intra-cellular 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 bacteria. The precise mechanism of action of metronidazole is unclear.

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.

Antimicrobial activity

Bacteroides species
Gardnerella vaginalis
Mobiluncus species
Peptostreptococcus species

Susceptibility Testing
For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

INDICATIONS AND USAGE

Bacterial Vaginosis (BV). FLAGYL ER 750 mg tablets are indicated in the treatment of BV in non-pregnant women.

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

FLAGYL ER 750 mg tablets are contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

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**).

Cockayne Syndrome

FLAGYL ER 750 mg tablets are contraindicated in patients with Cockayne syndrome. Severe irreversible hepatotoxicity/acute liver failure with fatal outcomes have been reported after initiation of metronidazole in patients with Cockayne syndrome (see **ADVERSE REACTIONS**).

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. FLAGYL ER tablets should not be administered to patients with severe (Child-Pugh C) hepatic impairment unless it is deemed that the benefits outweigh the risks in these patients. For patients with mild to moderate hepatic impairment, no dosage adjustment is needed. Patients with hepatic impairment who receive the usual recommended dose of FLAGYL ER tablets 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 leucopenia 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 FLAGYL ER in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria 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 Infections

Patients should be counseled that FLAGYL ER should only be used to treat bacterial infections. FLAGYL ER does not treat viral infections (e.g., the common cold). When FLAGYL ER 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 FLAGYL ER 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 2 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 FLAGYL 375 capsules 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 been reported.

Drugs that Prolong the QT interval

QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

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 ($NAD^+ \rightleftarrows NADH$). 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, lung, 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^2 (about 3 times the recommended daily dose, based on body surface area comparisons). Malignant lymphomas and pulmonary neoplasms are 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 (approximately 5 times the recommended 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:

There are no adequate and well-controlled studies of FLAGYL ER 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 finding 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 about four times the 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. There are no data on the effects of metronidazole on milk production. Animal studies have shown the potential for tumorigenicity after oral metronidazole was administered chronically to rats and mice (see **PRECAUTIONS**, Carcinogenesis, Mutagenesis, Impairment of Fertility). This drug is not intended to be administered chronically; therefore, the clinical relevance of the findings of the animal studies is unclear. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FLAGYL and any potential adverse effects on the breastfed infant from FLAGYL or from the underlying maternal condition. Alternatively, a nursing mother may choose to pump and discard human milk for the duration of FLAGYL therapy, and for 48 hours after the last dose and feed her infant stored human milk or formula.

Geriatric use

In 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

The safety and efficacy of FLAGYL ER 750 mg tablets in the treatment of bacterial vaginosis in post-menarchal females has been established on the extrapolation of clinical trial data from adult women. The safety and efficacy of FLAGYL ER 750 mg tablets in pre-menarchal females have not been established.

ADVERSE REACTIONS

In two multicenter clinical trials, a total of 270 patients received 750 mg FLAGYL ER tablets orally once daily for 7 days, and 287 were treated with a comparator agent administered intravaginally once daily for 7 days (See **CLINICAL STUDIES).**[3,4]

Most adverse events were described as being of mild or moderate severity. Among patients taking FLAGYL ER who reported headaches, 10% considered them severe, and less than 2% of reported episodes of nausea were considered severe. Metallic taste was reported by 9% of patients taking FLAGYL ER.

Adverse events reported at ≥2% incidence for either treatment group, irrespective of treatment causality, are summarized in the table below.

Adverse Events
(≥2% Incidence Rate)—Irrespective of Treatment Causality

	FLAGYL ER 7 days (N=267)	Vaginal Preparation (N=285)
Headache	48 (18%)	44 (15%)
Vaginitis	39 (15%)	32 (12%)
Nausea	28 (10%)	8 (3%)
Taste Perversion (metallic taste)	23 (9%)	1 (0%)
Infection Bacterial	19 (7%)	17 (6%)
Influenza-like Symptoms	17 (6%)	20 (7%)
Pruritus Genital	14 (5%)	25 (9%)
Abdominal Pain	10 (4%)	13 (5%)
Dizziness	11 (4%)	3 (1%)
Diarrhea	11 (4%)	3 (1%)
Upper Respiratory Tract Infection	11 (4%)	10 (4%)
Rhinitis	12 (4%)	10 (4%)
Sinusitis	7 (3%)	6 (2%)
Urine Abnormal	7 (3%)	4 (1%)
Pharyngitis	8 (3%)	4 (1%)
Dysmenorrhea	9 (3%)	7 (2%)
Moniliasis	9 (3%)	8 (3%)
Mouth Dry	5 (2%)	2 (1%)
Urinary Tract Infection	6 (2%)	16 (6%)

Vulvovaginal candidiasis is a recognized consequence of treatment with many anti-infective agents. In these multicenter clinical trials, there were no statistically significant differences in the incidence rates of yeast vaginitis for groups of patients treated with FLAGYL ER or the vaginal comparator.

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; 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: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval. 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.

Hepatic: Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne syndrome (latency from drug start to signs of liver failure as short as 2 days) (see **CONTRAINDICATIONS**).

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 FLAGYL ER 750 mg 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 g 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

Bacterial Vaginosis: 750 mg once daily by mouth for seven consecutive days.

FLAGYL ER 750 mg tablets should be taken under fasting conditions, at least one hour before or two hours after meals. The optimum extended-release characteristics of FLAGYL ER 750 mg are obtained when the drug is taken under fasting conditions (See **CLINICAL PHARMACOLOGY,** Absorption).
FLAGYL ER tablets should not be split, chewed, or crushed.

Dosage Adjustments

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 a 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

FLAGYL ER 750 mg tablets are oval, blue, film coated, with SEARLE and 1961 embossed on one side and FLAGYL and ER on the other side, supplied as:

NDC Number	Size
0025–1961–30	Bottle of 30

Storage and Stability: Store in a dry place at 25°C (77°F); excursions permitted to 15°-30°C (59°–86°F). [See USP Controlled Room Temperature.] Dispense in a well-closed container with a child-resistant closure.

CLINICAL STUDIES

Bacterial vaginosis (BV) is a clinical syndrome that results from a replacement of the normal, *Lactobacillus*-dominant flora with several other organisms including

Gardnerella vaginalis, *Mobiluncus* spp, *Mycoplasma hominis* and anaerobes (*Peptostreptococcus* spp and *Bacteroides* spp).

FLAGYL ER was studied in patients with BV in two randomized, multicenter, well-controlled, investigator blind clinical trials.[3,4] A total of 557 otherwise healthy nonpregnant patients with BV were randomized to treatment with FLAGYL ER once a day for 7 days (n=270) or 2% clindamycin vaginal cream one applicator full (5 grams) once a day for 7 days (n=287).

The primary efficacy endpoint for each treatment regimen was defined as clinical cure assessed at 28–32 days post-therapy. Clinical cure was defined as a return to normal of the vaginal pH (≤4.5), absence of a "fishy" amine odor, and absence of clue cells.

The study results are presented in the table below:

Clinical Cure Rates at One Month

	FLAGYL ER % (n/N)	**2% clindamycin cream % (n/N)**
Study 1	61% (77/126)	59% (80/135)
Study 2	62% (74/119)*	43% (50/117)

*$p<0.05$ versus clindamycin cream

At one month post-therapy the pH of the vagina returned to normal earlier and in a greater percentage of patients in the FLAGYL ER treatment group when compared to the 2% clindamycin vaginal cream group; 72% vs. 65%, respectively. Likewise, FLAGYL ER restored the normal *Lactobacillus*-predominant vaginal flora in a larger percentage of patients at one month post-therapy when compared to the 2% clindamycin treated group; 74% vs. 63%, respectively.

REFERENCES

1. Salas-Herrera IG, Pearson RM, Johnston A, and Turner P. Concentration of metronidazole in cervical mucus and serum after single and repeated oral doses. *J Antimicrobial Chemotherapy* 1991; 28:283–289.

2. Metronidazole modified-release tablet multiple-dose bioequivalency study (fed/fasting). G.D. Searle & Co., Protocol No. S13-94-02-014; Report No. S13-95-06-014, 11 July 1995.

3. Integrated clinical and statistical report for the treatment of bacterial vaginosis with metronidazole modified release tablet— a dose duration study. G.D. Searle & Co., Protocol No. N13-95-02-015; Report No. N13-96-06-015, 19 Nov 1996.

4. Integrated clinical and statistical report for the treatment of bacterial vaginosis with metronidazole modified release tablet. G.D. Searle & Co., Protocol No. N13-95-02-017; Report No. N13-96-06-017, 11 Nov 1996.

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This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

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