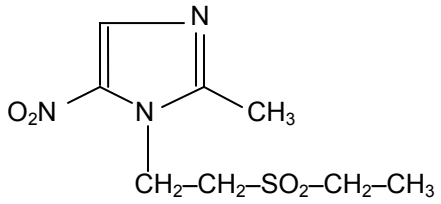
Tindamax™
(tinidazole tablets)

Carcinogenicity has been seen in mice and rats treated chronically with another agent in the nitroimidazole class (metronidazole). (See PRECAUTIONS). Although such data have not been reported for tinidazole, unnecessary use of tinidazole should be avoided. Its use should be reserved for the conditions described in INDICATIONS AND USAGE.

DESCRIPTION

Tinidazole is a synthetic antiprotozoal agent. It is 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole, a second-generation 2-methyl-5-nitroimidazole, which has the following chemical structure:



Tindamax pink film-coated oral tablets contain 500 mg or 250 mg of tinidazole. Inactive ingredients include croscarmellose sodium, FD&C Red 40 lake, FD&C Yellow 6 lake, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized corn starch, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY

Absorption

After oral administration, tinidazole is rapidly and completely absorbed. A bioavailability study of Tindamax tablets was conducted in adult healthy volunteers. All subjects received a single oral dose of 2 g (four 500 mg tablets) of tinidazole following an overnight fast. Oral administration of four 500 mg tablets of Tindamax under fasted conditions produced a mean peak plasma concentration (C_{max}) of 47.7 (±7.5) µg/mL with a mean time to peak concentration (T_{max}) of 1.6 (±0.7) hours and a mean area under the plasma concentration-time curve (AUC, 0-∞) of 901.6 (± 126.5) µg•hr/mL at 72 hours. The elimination half-life ($T_{1/2}$) was 13.2 (±1.4) hours. Mean plasma levels decreased to 14.3 µg/mL at 24 hours, 3.8 µg/mL at 48 hours and 0.8 µg/mL at 72 hours following administration. Steady-state conditions are reached in 2½ - 3 days of multi-day dosing. Administration of Tindamax tablets with food resulted in a delay in T_{max} of approximately 2 hours and a decline in C_{max} of approximately 10%, compared to fasted conditions. However, administration of Tindamax with food did not affect AUC or $T_{1/2}$ in this study.

In healthy volunteers, administration of crushed Tindamax tablets in artificial cherry syrup, prepared as described below, after an overnight fast has no effect on any pharmacokinetic parameter as compared to tablets swallowed whole under fasted conditions.

Procedure for extemporaneous pharmacy compounding of the oral suspension: Four 500 mg oral tablets were ground to a fine powder with a mortar and pestle. Approximately 10 mL of cherry syrup were added to the powder and mixed until smooth. The suspension was transferred to a graduated amber container. Several small rinses of cherry syrup were used to transfer any remaining drug in the mortar to the final suspension for a final volume of 30 mL. The suspension of crushed tablets in artificial cherry syrup (Humco®) is stable for 7 days at room temperature. When this suspension is used, it should be shaken well before each administration.

Distribution

Tinidazole is distributed into virtually all tissues and body fluids and also crosses the blood-brain barrier. The apparent volume of distribution is about 50 liters. Plasma protein binding of tinidazole is 12%.

Tinidazole crosses the placental barrier and is secreted in breast milk (see **PRECAUTIONS/Pregnancy** and **PRECAUTIONS/Nursing mothers**).

Metabolism
Tinidazole, like metronidazole, is significantly metabolized in humans prior to excretion. Tinidazole is partly metabolized by oxidation, hydroxylation and conjugation. Tinidazole is the major drug-related constituent in plasma after human treatment, along with a small amount of the 2-hydroxymethyl metabolite.

Tinidazole is biotransformed mainly by CYP3A4. In an *in vitro* metabolic drug interaction study, tinidazole concentrations of up to 75 µg/mL did not inhibit the enzyme activities of CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4.

The potential of tinidazole to induce the metabolism of other drugs has not been evaluated.

Elimination
The plasma half-life of tinidazole is approximately 12-14 hours. Tinidazole is excreted by the liver and the kidneys. Tinidazole is excreted in the urine mainly as unchanged drug (approximately 20-25% of the administered dose). Approximately 12% of the drug is excreted in the feces.

Pharmacokinetics in Special Populations
Patients with impaired renal function: The pharmacokinetics of tinidazole in patients with severe renal impairment (CrCL < 22 mL/min) are not significantly different from the pharmacokinetics seen in healthy subjects. However, during hemodialysis, clearance of tinidazole is significantly increased; the half-life is reduced from 12.0 hours to 4.9 hours. Approximately 43% of the amount present in the body is eliminated during a 6-hour hemodialysis session. The pharmacokinetics of tinidazole in patients undergoing routine continuous peritoneal dialysis have not been investigated. (See **DOSAGE AND ADMINISTRATION**).

Patients with impaired hepatic function: There are no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduction of metabolic elimination of metronidazole, a chemically-related nitroimidazole, in patients with hepatic dysfunction has been reported in several studies. (See **DOSAGE AND ADMINISTRATION**).

MICROBIOLOGY

Mechanism of Action: Tinidazole is an antiprotozoal agent. The nitro group of tinidazole is reduced by cell extracts of *Trichomonas*. The free nitro radical generated as a result of this reduction may be responsible for the antiprotozoal activity. The mechanism by which tinidazole exhibits activity against *Giardia* and *Entamoeba* species is not known.

Activity *in vitro* and *in vivo*: Tinidazole demonstrates activity both *in vitro* and in clinical infections against the following protozoa:
Trichomonas vaginalis
Giardia duodenalis (also termed *G. lamblia*)
Entamoeba histolytica

Tinidazole does not appear to have activity against most strains of vaginal lactobacilli.

Susceptibility Tests
For protozoal parasites, standardized tests do not exist for use in clinical microbiology laboratories.

Drug Resistance
The development of resistance to tinidazole by *T. vaginalis*, *G. duodenalis* or *E. histolytica* has not been examined.

Cross-resistance
Approximately 38% of *T. vaginalis* isolates exhibiting reduced susceptibility to metronidazole also show reduced susceptibility to tinidazole *in vitro*. The clinical significance of such an effect is not known.

INDICATIONS AND USAGE

Trichomoniasis: Tindamax oral tablets are indicated for the treatment of trichomoniasis caused by *T. vaginalis* in both female and male patients. The organism should be identified by appropriate diagnostic procedures. Because trichomoniasis is a sexually transmitted disease with potentially serious sequelae, partners of infected patients should be treated simultaneously in order to prevent re-infection.

Giardiasis: Tindamax oral tablets are indicated for the treatment of giardiasis caused by *G. duodenalis* (also termed *G. lamblia*) in both adults and pediatric patients older than three years of age.

Amebiasis: Tindamax oral tablets are indicated for the treatment of intestinal amebiasis and amebic liver abscess caused by *E. histolytica* in both adults and pediatric patients older than three years of age. It is not indicated in the treatment of asymptomatic cyst passage.

CONTRAINDICATIONS

Tindamax is contraindicated in patients with hypersensitivity to tinidazole, any component of the tablet, or other nitroimidazole derivatives. Tindamax is contraindicated during the first trimester of pregnancy. See **PRECAUTIONS/Nursing mothers**.

WARNINGS

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with nitroimidazole drugs including tinidazole and metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of Tindamax therapy. Tinidazole should be administered with caution to patients with central nervous system diseases.

PRECAUTIONS

General:
Tinidazole is a nitroimidazole and should be used with caution in patients with evidence of or history of blood dyscrasia.
The disposition of tinidazole in patients with hepatic impairment has not been evaluated. Patients with severe hepatic disease metabolize nitroimidazoles slowly, with resultant accumulation of parent drug in the plasma. Accordingly, for patients with hepatic dysfunction, usual recommended doses of tinidazole should be administered cautiously.
Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with tinidazole and requires treatment with an antifungal agent.

Information for patients:
Tindamax tablets should be taken with food (see **DOSAGE AND ADMINISTRATION**).
Alcoholic beverages should be avoided while taking Tindamax and for three days afterward (see **PRECAUTIONS/Drug interactions**).

Laboratory tests:
Tinidazole, like metronidazole, may produce transient leukopenia and neutropenia; however, no persistent hematological abnormalities attributable to tinidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended if retreatment is necessary.

Drug interactions:
Although not studied specifically for tinidazole, the following drug interactions were reported for metronidazole, a chemically-related nitroimidazole. Therefore, these drug interactions may occur with tinidazole.

Potential effect of tinidazole on other drugs

Warfarin and other oral coumarin anticoagulants. As with other nitroimidazole derivatives, tinidazole may enhance the effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. This potential interaction should be considered when tinidazole is prescribed for patients on this type of anticoagulant therapy. The dosage of oral anticoagulants may need to be adjusted during tinidazole co-administration and up to 8 days after discontinuation.

Alcohols, Disulfiram. Alcoholic beverages and preparations containing ethanol or propylene glycol should be avoided during tinidazole therapy and for three days afterward because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Psychotic reactions have been reported in alcoholic patients using metronidazole and disulfiram concurrently. Though no similar reactions have been reported with tinidazole, tinidazole should not be given to patients who have taken disulfiram within the last two weeks.

Lithium. Metronidazole has been reported to elevate serum lithium levels. It is not known if tinidazole shares this property with metronidazole, but consideration should be given to measuring serum lithium and creatinine levels after several days of simultaneous lithium and tinidazole treatment to detect potential lithium intoxication.

Phenytoin, Fosphenytoin. Fosphenytoin is a pro-drug of phenytoin. Concomitant administration of oral metronidazole and intravenous phenytoin was reported to result in prolongation of the half-life and reduction in the clearance of phenytoin. Metronidazole did not significantly affect the pharmacokinetics of orally-administered phenytoin.

Cyclosporine, Tacrolimus. There are several case reports suggesting that metronidazole has the potential to increase the levels of cyclosporine and tacrolimus. During tinidazole co-administration with either of these drugs, the patient should be monitored for signs of calcineurin-inhibitor associated toxicities.

Fluorouracil. Metronidazole was shown to decrease the clearance of fluorouracil, resulting in an increase in side-effects without an increase in therapeutic benefits. If the concomitant use of tinidazole and fluorouracil cannot be avoided, the patient should be monitored for fluorouracil-associated toxicities.

Potential effect of other drugs on tinidazole

Simultaneous administration of tinidazole with drugs that induce liver microsomal enzymes (cytochrome P-450) such as *phenobarbital, rifampin*, *phenytoin* and *fosphenytoin* (a pro-drug of phenytoin) may accelerate the elimination of tinidazole, decreasing the plasma level of tinidazole. Simultaneous administration of drugs that inhibit the activity of liver microsomal enzymes, such as *cimetidine* and *ketoconazole*, may prolong the half-life and decrease the plasma clearance of tinidazole, increasing the plasma level of tinidazole.

Cholestyramine. Cholestyramine was shown to decrease the oral bioavailability of metronidazole by 21%. Thus, it is advisable to separate dosing of cholestyramine and tinidazole to minimize any potential effect on the oral bioavailability of tinidazole.

Oxytetracycline. Oxytetracycline was reported to antagonize the therapeutic effect of metronidazole.

Drug/Laboratory test interactions: Tinidazole, like metronidazole, may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide adenine dinucleotide ($NAD^+ \leftrightarrow$ NADH). Potential interference is due to the similarity of absorbance peaks of NADH and tinidazole.

Carcinogenesis, Mutagenesis, Impairment of fertility:

Metronidazole, a chemically-related nitroimidazole, has been reported to be carcinogenic in mice and rats but not hamsters. In several studies metronidazole showed evidence of pulmonary, hepatic and lymphatic

tumorigenesis in mice and mammary and hepatic tumors in female rats. Tinidazole carcinogenicity studies in rats, mice or hamsters have not been reported.

Tinidazole was mutagenic in the TA 100, *S. typhimurium* tester strain both with and without the metabolic activation system and was negative for mutagenicity in the TA 98 strain. Mutagenicity results were mixed (positive and negative) in the TA 1535, 1537 and 1538 strains. Tinidazole was also mutagenic in a tester strain of *Klebsiella pneumonia*. Tinidazole was negative for mutagenicity in a mammalian cell culture system utilizing Chinese hamster lung V79 cells (HGPRT test system) and negative for genotoxicity in the Chinese hamster ovary (CHO) sister chromatid exchange assay. Tinidazole was positive for *in vivo* genotoxicity in the mouse micronucleus assay.

In a 60-day fertility study, tinidazole reduced fertility and produced testicular histopathology in male rats at a 600 mg/kg/day dose level (approximately 3-fold the highest human therapeutic dose based upon body surface area conversions). Spermatogenic effects resulted from 300 and 600 mg/kg/day dose levels. The no observed adverse effect level for testicular and spermatogenic effects was 100 mg/kg/day (approximately 0.5-fold the highest human therapeutic dose based upon body surface area conversions). This effect is characteristic of agents in the 5-nitroimidazole class.

Pregnancy:
Teratogenic effects: Pregnancy Category C
The use of tinidazole in pregnant patients has not been studied. Since Tinidazole crosses the placental barrier and enters fetal circulation it should not be administered to pregnant patients in the first trimester. Embryo-fetal developmental toxicity studies in pregnant mice indicated no embryo-fetal toxicity or malformations at the highest dose level of 2,500 mg/kg (approximately 6.3-fold the highest human therapeutic dose based upon body surface area conversions). In a study with pregnant rats a slightly higher incidence of fetal mortality was observed at a maternal dose of 500 mg/kg (2.5-fold the highest human therapeutic dose based upon body surface area conversions). No biologically relevant neonatal developmental effects were observed in rat neonates following maternal doses as high as 600 mg/kg (3-fold the highest human therapeutic dose based upon body surface area conversions). Because animal reproduction studies are not always predictive of human response and because there is some evidence of mutagenic potential, the use of tinidazole during pregnancy requires that the potential benefits of the drug be weighed against the possible risks to both the mother and the fetus. (See **CONTRAINDICATIONS**).

Nursing mothers: Tinidazole is excreted in breast milk in concentrations similar to those seen in serum. Tinidazole can be detected in breast milk for up to 72 hours following administration. Interruption of breast-feeding is recommended during tinidazole therapy and for three days following the last dose.

Pediatric use: Other than for use in the treatment of giardiasis and amebiasis in pediatric patients older than three years of age, safety and effectiveness of tinidazole in pediatric patients have not been established.

Geriatric use: Clinical studies of tinidazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Among 3,669 patients treated with a single 2 g dose of tinidazole, in both controlled and uncontrolled trichomoniasis and giardiasis clinical studies, adverse effects were reported by 11.0% of patients. For multi-day dosing in controlled and uncontrolled amebiasis studies, adverse effects were reported by 13.8% of 1,765 patients. Reported adverse effects from clinical trials have generally been mild and self-limiting. Common (≥ 1% incidence) adverse effects reported by body system are as follows. (Note: Data described below are pooled from studies with variable designs and safety evaluations.)

	2 g	Multi-day dose
GI		
Metallic/bitter taste	3.7%	6.3%
Nausea	3.2%	4.5%
Anorexia	1.5%	2.5%
Dyspepsia/cramps/epigastric discomfort	1.8%	1.4%
Vomiting	1.5%	0.9%
Constipation	0.4%	1.4%
CNS		
Weakness/fatigue/malaise	2.1%	1.1%
Dizziness	1.1%	0.5%
Other		
Headache	1.3%	0.7%
Total patients with adverse effects	11.0% (403/3669)	13.8% (244/1765)

Other adverse effects reported with tinidazole include:
Central Nervous System: Two serious adverse reactions reported include convulsions and transient peripheral neuropathy including numbness and paresthesia. Other CNS reports include vertigo, ataxia, giddiness, insomnia, drowsiness.
Gastrointestinal: tongue discoloration, stomatitis, diarrhea
Hypersensitivity: urticaria, pruritis, rash, flushing, sweating, dryness of mouth, fever, burning sensation, thirst, salivation, angioedema
Renal: darkened urine
Cardiovascular: palpitations
Hematopoietic: transient neutropenia, transient leukopenia
Other: candida overgrowth, increased vaginal discharge, oral candidiasis, hepatic abnormalities including raised transaminase level, arthralgias, myalgias, arthritis
Rare reported adverse effects include bronchospasm, dypsnea, coma, confusion, depression, furry tongue, pharyngitis and reversible thrombocytopenia.

Adverse Reactions in Pediatric Patients: Among 6 pooled pediatric studies, 287 patients between the ages of 4 months and 11 years were evaluated. Adverse events reported in pediatric patients taking tinidazole were similar in nature and frequency to adult findings including nausea, vomiting, diarrhea, taste change, anorexia and abdominal pain.

OVERDOSAGE

There are no reported overdoses with tinidazole in humans. In acute studies with mice and rats, the LD_{50} for mice was generally > 3,600 mg/kg for oral administration and was > 2,300 mg/kg for intraperitoneal administration. In rats, the LD_{50} was > 2,000 mg/kg for both oral and intraperitoneal administration.

Treatment of overdosage
There is no specific antidote for the treatment of overdosage with tinidazole; therefore, treatment should be symptomatic and supportive. Gastric lavage may be helpful. Hemodialysis can be considered because approximately 43% of the amount present in the body is eliminated during a 6-hour hemodialysis session.

DOSAGE AND ADMINISTRATION

As with metronidazole, it is advisable to take tinidazole with food to minimize the incidence of epigastric discomfort and other gastrointestional side-effects. Food does not affect the oral bioavailability of tinidazole.

Trichomoniasis: In both females and males, a single 2 g oral dose taken with food. Since trichomoniasis is a sexually transmitted disease, sexual partners should be treated with the same dose and at the same time.

Giardiasis: In adults, a single 2 g dose taken with food. In pediatric patients older than three years of age, a single dose of 50 mg/kg (up to 2 g) with food.

Amebiasis:
Intestinal: In adults, a 2 g dose per day for 3 days taken with food. In pediatric patients older than three years of age, 50 mg/kg/day (up to 2 g per day) for 3 days with food.
Amebic liver abscess: In adults, a 2 g dose per day for 3-5 days taken with food. In pediatric patients older than three years of age, 50 mg/kg/day (up to 2 g per day) for 3-5 days with food. There are limited pediatric data on durations of therapy exceeding 3 days, although a small number of children were treated for 5 days without reported adverse events. Children should be closely monitored when treatment durations exceed 3 days.

Pediatric Administration: For those unable to swallow tablets, Tindamax tablets may be crushed in artificial cherry syrup, to be taken with food. See **CLINICAL PHARMACOLOGY** for procedure for extemporaneous pharmacy compounding of the oral suspension, as used in clinical pharmacology studies.

Patients with impaired renal function: Tinidazole pharmacokinetics in patients with significantly impaired renal function are not significantly different than those seen in healthy subjects. Therefore, no dose adjustments are necessary in these patients.

Patients undergoing hemodialysis: During hemodialysis, clearance of tinidazole is significantly increased; the half-life is reduced from 12.0 hours to 4.9 hours. Approximately 43% of the amount present in the body is eliminated during a 6-hour hemodialysis session. Thus, if tinidazole is administered on a day when dialysis is performed, it is recommended that an additional dose of tinidazole equivalent to one-half of the recommended dose be administered after the end of the hemodialysis.
The pharmacokinetics of tinidazole in patients undergoing routine continuous peritoneal dialysis have not been investigated. (See **CLINICAL PHARMACOLOGY/Special Populations**).

Patients with impaired hepatic function: There are no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduction of metabolic elimination of metronidazole, a chemically-related nitroimidazole, in patients with hepatic dysfunction has been reported in several studies. In the absence of data on tinidazole, usually recommended doses of tinidazole should be administered cautiously in such patients.

HOW SUPPLIED

Tindamax 500 mg tablets are pink, caplet-shaped, film-coated, scored tablets, with P L debossed on one side and 500 on the other, supplied in bottles with child-resistant caps as:

NDC 66378-500-20	Bottle of 20
NDC 66378-500-60	Bottle of 60

Tindamax 250 mg tablets are pink, round, film-coated, scored tablets, with P L debossed on one side and 250 on the other, supplied in bottles with child-resistant caps as:

NDC 66378-250-40	Bottle of 40
NDC 66378-250-44	Bottle of 100

Storage and stability
Store at controlled room temperature 20-25º C (68-77º F); excursions permitted to 15-30º C (59-86º F) [see USP]. Protect contents from light.

CLINICAL STUDIES

Trichomoniasis
Tinidazole (2 g single oral dose) use in trichomoniasis has been well documented in 34 published reports from the world literature involving over 2,800 patients treated with tinidazole. In four published, blinded, randomized, comparative studies of the 2 g tinidazole single oral dose where efficacy was assessed by culture at time points post-treatment ranging from one week to one month, reported cure rates ranged from 92% (37/40) to 100% (65/65) (n=172 total subjects). In four published, blinded, randomized, comparative studies where efficacy was assessed by wet mount between 7-14 days post-treatment, reported cure rates ranged from 80% (8/10) to 100% (16/16) (n=116 total subjects). In these studies, tinidazole was superior to

placebo and comparable to other anti-trichomonal drugs. The single oral 2 g tinidazole dose was also assessed in four open label trials in men (one comparative to metronidazole and 3 single arm studies). Parasitological evaluation of the urine was performed both pre- and post-treatment and reported cure rates ranged from 83% (25/30) to 100% (80/80) (n=142 total subjects).

Giardiasis
Tinidazole (2 g single dose) use in giardiasis has been documented in 19 published reports from the world literature involving over 1,600 patients (adults and pediatric patients). In eight controlled studies involving a total of 619 subjects of whom 299 were given the 2 g x 1 day (50 mg/kg x 1 day in pediatric patients) oral dose of tinidazole, reported cure rates ranged from 80% (40/50) to 100% (15/15). In three of these trials where the comparator was 2 to 3 days of various doses of metronidazole, reported cure rates for metronidazole were 76% (19/25) to 93% (14/15). Data comparing a single 2 g dose of tinidazole to usually recommended 5-7 days of metronidazole are limited.

Intestinal Amebiasis
Tinidazole use in intestinal amebiasis has been documented in 26 published reports from the world literature involving over 1,400 patients. Most reports utilized tinidazole 2 g/day x 3 days. In four published, randomized, controlled studies (1 investigator single-blind, 3 open-label) of the 2 g/day x 3 days oral dose of tinidazole, reported cure rates after three days of therapy among a total of 220 subjects ranged from 86% (25/29) to 93% (25/27).

Amebic Liver Abscess
Tinidazole use in amebic liver abscess has been documented in 18 published reports from the world literature involving over 470 patients. Most reports utilized tinidazole 2 g/day x 2-5 days. In seven published, randomized, controlled studies (1 double-blind, 1 single-blind, 5 open-label) of the 2 g/day x 2-5 days oral dose of tinidazole accompanied by aspiration of the liver abscess when clinically necessary, reported cure rates among 133 subjects ranged from 81% (17/21) to 100% (16/16). Four of these studies utilized at least 3 days of tinidazole.

Manufactured for Presutti Laboratories, Inc., Arlington Heights, IL 60004 by Mikart, Inc., Atlanta, GA.

Revised: May 14, 2004

Rx Only