NDC XXXXX-XXX-XX

Tinidazole Tablets

250 mg

Rx only 40 Tablets

PACK PHARMACEUTICALS, LLC

Each film-coated tablet contains:
Tinidazole USP ..... 250 mg

Usual Dosage: See accompanying Prescribing Information

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

WARNING: As with all medications, keep out of reach of children.

M.L. G / 1430

Manufactured in India by: Unique Pharmaceutcal Laboratories (A Div. of J. B. Chemicals & Pharmaceuticals Ltd.) Mumbai - 400 030.

Distributed by: PACK Pharmaceuticals, LLC
Buffalo Grove, IL 60089

XXXXXX

BARCODE

Lot No.:

Exp. Date:

NDC XXXXX-XXX-XX

Tinidazole Tablets

500 mg

Rx only 20 Tablets

PACK PHARMACEUTICALS LLC

Each film-coated tablet contains:
Tinidazole USP ..... 500 mg

Usual Dosage: See accompanying Prescribing Information

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

WARNING: As with all medications, keep out of reach of children.

M.L. G / 1430

Manufactured in India by: Unique Pharmaceutical Laboratories (A Div. of J. B. Chemicals & Pharmaceuticals Ltd.) Mumbai - 400 030.

Distributed by: PACK Pharmaceuticals, LLC Buffalo Grove, IL 60089

XXXXX

BARCODE

Lot No.:

Exp. Date:

NDC XXXXX-XXX-XX

Tinidazole Tablets

500 mg

℞ only 60 Tablets

PACK PHARMACEUTICALS, LLC

Each film-coated tablet contains:
Tinidazole USP ..... 500 mg

Usual Dosage: See accompanying Prescribing information

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

WARNING: As with all medications, keep out of reach of children.

M.L. G / 1430

BARCODE

Manufactured in India by: Unique Pharmaceutical Laboratories (A Div. of J. B. Chemicals & Pharmaceuticals Ltd.) Mumbai - 400 030.

Distributed by: PACK Pharmaceuticals, LLC
Buffalo Grove, IL 60089

xxxxxx

Lot No.:

Exp. Date:

TINIDAZOLE TABLETS 250 mg and 500 mg

HIGHLIGHTS OF PRESCR B NG

These highlights do not include all the information needed to use Tinidazole Tablets safely and effectively. See full prescribing information for Tinidazole Tablets

Tinidazole Tablets for oral use

Initial U.S. Approval: 2004

To reduce the development of drug resistant bacteria and maintain the effectiveness of Tinidazole Tablets and other antibacterial drugs, Tinidazole Tablets should be used only to reat or prevent infections that are proven or strongly suspected to be caused by bacteria

WARNING: POTENTIAL RISK FOR CARCINOGENICITY

See full prescribing information for complete boxed warning.

Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent (13 1). Although such data have not been reported for tinidazole, the two drugs are structurally related and have sim lar biologic effects. Use should be imited to approved indications only.

RECENT MAJOR CHANGES

Indica ions and Usage, Bacterial Vaginosis (1 4) 5/2007
Dosage and Administration, Bacterial Vaginosis (2 6) 5/2007

INDICATIONS AND USAGE

Tinidazole Tablets is a nitroimidazole an imicrobial indicated for

- Trichomoniasis (1 1)
- Giardiasis in pa ients age 3 and older (1 2)
- Amebiasis in patients age 3 and older (1 3)
- Bacterial Vaginosis in non pregnant, adult women (1 4, 8 1)

DOSAGE AND ADM N STRATION

- Trichomoniasis a single 2 g oral dose aken wi h food Treat sexual partners with the same dose and at the same time (2 3)
- Giardiasis Adults a single 2 g dose aken wi h food Pediatric patients older than hree years of age a single dose of 50 mg/kg (up o 2 g) with food (2 4)
- Amebiasis, *Intestinal* Adults 2 g per day for 3 days with food Pediatric patients older han three years of age 50 mg/kg/day (up to 2 g per day) for 3 days with food (2 5)
- Amebic iver abscess Adults 2 g per day for 3 5 days with food Pediatric patients older than three years of age 50 mg/kg/day (up to 2 g per day) for 3 5 days with food (2 5)
- Bacterial vaginosis Non pregnant, adult women 2 g once daily for 2 days taken with food, or 1 g once da ly for 5 days taken with food (2 6)

DOSAGE FORMS AND STRENGTHS

Tablets 250 mg and 500 mg (3)

CONTRAINDICATIONS

- Prior history of hypersensi ivity to inidazole or other nitroimidazole derivatives (4, 6 1,6 2)
- First trimester of pregnancy (4, 8 1)
- Nursing mothers, unless breast feeding is interrupted during tinidazole therapy and for 3 days following the last dose (4, 8 3)

WARNINGS AND PRECAUTIONS

- Seizures and neuropa hy have been reported Discontinue Tinidazole Table s if abnormal neurologic signs develop (5 1)
- Vaginal candidiasis may develop with Tinidazole Tablets and require treatment wi h an antifungal agent (5 2)
- Use Tinidazole Table s wi h caution in patients wi h blood dyscrasias Tinidazole Tablets may produce transient leukopenia and neu ropenia (5 3, 7 3)

ADVERSE REACTIONS

Most common adverse reactions for a single 2 g dose of inidazole (incidence >1%) are metallic/bitter taste, nausea, weakness/fatigue/malaise, dyspepsia/cramps/epigastric discomfort, vomiting, anorexia, headache, dizziness and constipa ion (6 1)

To report SUSPECTED ADVERSE REACTIONS, contact PACK Pharmaceuticals, LLC at 847 2290153 or FDA at 1 800 FDA 1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

The following drug interactions were reported for metronidazole, a chemically related nitroimidazole and may therefore occur with tinidazole

- Warfarin and other oral coumarin anticoagulants Anticoagulant dosage may need adjustment during and up to 8 days after tinidazole therapy (7 1)
- Alcohol containing beverages/preparations Avoid during and up to 3 days after tinidazole therapy (7 1)
- Lithium Monitor serum lithium concentrations (7 1)
- Cyclosporine, tacrolimus Monitor for oxicities of hese immunosuppressive drugs (7 1)
- Fluorouracil Monitor for fluorouracil associated toxicities (7 1)
- Phenytoin, fosphenytoin Adjus ment of an iconvulsant and/or tinidazole dose(s) may be needed (7 1, 7 2)
- CYP3A4 inducers/inhibitors Monitor for decreased tinidazole e fect or increased adverse reac ions (7 2)

USE N SPEC FIC POPULATIONS

- Pediatric Use Data on inidazole use in children is limi ed to treatment of giardiasis and amebiasis in patien s age 3 and older (8 4)
- Hemodialysis patients If tinidazole is administered the same day and prior to hemodialysis, adminis er an additional ½ dose after end of hemodialysis (8 6, 12 3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2010

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL RISK FOR CARC NOGENICITY

Carcinogenicity has been seen in mice and rats trea ed chronica ly with metronidazole, another ni roimidazole agent (13 1) Although such data have not been reported for tinidazole, the two drugs are structurally related and have sim lar biologic effects **Its use should be reserved for the conditions described in INDICATIONS AND USAGE (1).**

1 NDICATIONS AND USAGE

1.1 Trichomoniasis

Tinidazole is indicated for the treatment of richomoniasis caused by Trichomonas vagina is The organism should be ident fied by appropriate diagnostic procedures Because richomoniasis is a sexually transmitted disease with poten ia ly serious sequelae, partners of infected patients should be treated simultaneously in order o prevent re infection *[see C inical Studies (14 1)]*

1.2 Giardiasis

Tinidazole is indicated for the treatment of giardiasis caused by Giardia duodenalis (also ermed G lamblia) in both adults and pediatric patients older than hree years of age *[see C inical Studies (14 2)]*

1.3 Amebiasis

Tinidazole is indicated for the treatment of intestinal amebiasis and amebic liver abscess caused by Entamoeba histolytica in bo h adults and pediatric patients older than three years of age It is not indica ed in the treatment of asymptomatic cyst passage *[see Clinical Studies (14 3, 14 4)]*

1.4 Bacterial Vaginosis

Tinidazole is indicated for the treatment of bac erial vaginosis (formerly referred to as *Haemoph lus vagini is, Gardnerella vaginitis, nonspecific vagini is,* or *anaerobic vaginosis*) in non pregnant women *[see Use in Specific Populations (8 1) and C inical Studies (14 5)]*

Other pathogens commonly associated with vulvovaginitis such as *Trichomonas vagina is, Chlamydia trachomatis, Neisseria gonorrhoeae, Candida albicans and Herpes simplex* virus should be ruled out

To reduce the development of drug resistant bacteria and maintain the effectiveness of Tinidazole Tablets and other antibacterial drugs, Tinidazole Tablets should be used only to reat or prevent infections that are proven or s rongly suspec ed to be caused by suscept ble bacteria When cul ure and suscep bi ity information are available, they should be considered in selecting or modifying antibac erial therapy In the absence of such data, local epidemiology and suscep ib lity patterns may contr bu e o he empiric selection of herapy

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

It is advisable to ake tinidazole with food to minimize he incidence of epigastric discomfort and other gastrointestinal side effects Food does not affect the oral bioavailabi ity of inidazole *[see Clinical Pharmacology (12 3)]*

Alcoho ic beverages should be avoided when taking tinidazole and for 3 days afterwards *[see Drug Interactions (7 1)]*

2.2 Compounding of the Oral Suspension

For those unable to swa low tablets, Tinidazole Tablets may be crushed in art ficial cherry syrup to be taken with food

Procedure for Extemporaneous Pharmacy Compounding of the Oral Suspension Pulverize four 500 mg oral table s with a mortar and pestle Add approximately 10 mL of cherry syrup to he powder and mix un il smooth Transfer he suspension to a graduated amber container Use several sma l rinses of cherry syrup to transfer any remaining drug in he mortar to the inal suspension for a final volume of 30 mL The suspension of crushed tablets in art ficial cherry syrup is stable for 7 days at room empera ure When this suspension is used, it should be shaken well before each administration

2.3 Trichomoniasis

The recommended dose in bo h females and males is a single 2 g oral dose taken wi h food Since richomoniasis is a sexua ly transmitted disease, sexual partners should be treated with the same dose and at the same time

2.4 Giardiasis

The recommended dose in adul s is a single 2 g dose taken with food In pediatric patients older than three years of age, the recommended dose is a single dose of 50 mg/kg (up to 2 g) with food

2.5 Amebiasis

Intestinal The recommended dose in adults is a 2 g dose per day for 3 days taken wi h food In pediatric patients older han three years of age, he recommended dose is 50 mg/kg/day (up to 2 g per day) for 3 days wi h food

Amebic Liver Abscess The recommended dose in adults is a 2 g dose per day for 3 5 days aken with food In pediatric pa ients older han three years of age, the recommended dose is 50 mg/kg/day (up to 2 g per day) for 3 5 days wi h food There are limi ed pediatric data on dura ions of therapy exceeding 3 days, although a sma l number of children were treated for 5 days without additional reported adverse reactions Ch ldren should be closely moni ored when treatment durations exceed 3 days

2.6 Bacterial Vaginosis

The recommended dose in non pregnant females is a 2 g oral dose once daily for 2 days aken with food or a 1 g oral dose once daily for 5 days taken with food The use of tinidazole in pregnant patients has not been studied for bac erial vaginosis

3 DOSAGE FORMS AND STRENGTHS

- 250 mg ablets are pink, circular, f lm coated scored tablets, wi h T | P debossed on one side and 250 on the other
- 500 mg ablets are pink, capsule shaped, film coa ed scored ablets, wi h T | P debossed on one side and 500 on the other

4 CONTRAINDICATIONS

The use of inidazole is contraindicated

- In patients wi h a previous history of hypersensitivity to tinidazole or other nitroimidazole deriva ives Reported reactions have ranged in severity from urticaria to S evens Johnson syndrome *[see Adverse Reactions (6 1, 6 2)]*
- During first trimester of pregnancy *[see Use in Specific Popula ions (8 1)]*
- In nursing mothers In erruption of breast feeding is recommended during inidazole therapy and for 3 days following he last dose *[see Use in Spec fic Populations (8 3)]*

5 WARN NGS AND PRECAUTIONS

5.1 Neurological Adverse Reactions

Convulsive seizures and peripheral neuropa hy, he la ter characterized mainly by numbness or paresthesia of an extremi y, have been reported in patients treated with Tinidazole Tablets The appearance of abnormal neurologic signs demands the prompt discontinua ion of inidazole therapy

5.2 Vaginal Candidiasis

The use of tinidazole may result in Candida vaginitis In a clinical s udy of 235 women who received tinidazole for bac erial vaginosis, a vaginal fungal infection developed in 11 (4 7%) of all study subjects *[see Clinical Studies (14 5)]*

5.3 Blood Dyscrasia

Tinidazole should be used with caution in patients with evidence of or history of blood dyscrasia *[see Drug Interac ions (7 3)]*

5.4 Drug Resistance

Prescribing Tinidazole Tablets in the absence of a proven or strongly suspec ed bac erial infec ion or a prophylactic indication is unl kely to provide benefit to the pa ient and increases the risk of the development of drug resis ant bacteria

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because c inical trials are conducted under widely varying conditions, adverse reac ion rates observed in the clinical trials of a drug cannot be directly compared o rates in he c inical trials of another drug and may not reflect the ra es observed in practice

Among 3669 patients treated with a single 2 g dose of tinidazole, in both controlled and uncontrolled trichomoniasis and giardiasis clinical studies, adverse reactions were reported by 11 0% of patients For multi day dosing in contro led and uncontrolled amebiasis studies, adverse reactions were reported by 13 8% of 1765 patien s Common (≥ 1% incidence) adverse reactions reported by body system are as fo lows (Note Da a described in Table 1 below are pooled from studies with variable designs and safety evaluations)

O her adverse reactions reported with tinidazole include

Central Nervous Sys em Two serious adverse reactions reported include convulsions and transient peripheral neuropathy including numbness and pares hesia *[see Warnings and Precautions (5 1)]* Other CNS repor s include vertigo, ataxia, giddiness, insomnia, drowsiness

Gastroin estinal tongue discoloration, stomati is, diarrhea

Hypersensitivity urticaria, pruri is, rash, flushing, sweating, dryness of mouth, fever, burning sensation, thirst, salivation, angioedema

Renal darkened urine

Cardiovascular palpitations

Hematopoietic transient neu ropenia, transient leukopenia

O her *Candida* overgrowth, increased vaginal discharge, oral candidiasis, hepatic abnormalities including raised transaminase level, arthralgias, myalgias, and arthritis

Table 1. Adverse Reactions Summary of Published Reports

	2 g single dose	Mul i day dose
Gl Me al ic bit er 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%
Cons ipation	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 reactions	11 0% (403/3669)	13 8% (244/1765)

Rare repor ed adverse reactions include bronchospasm, dyspnea, coma, confusion, depression, furry tongue, pharyngi is and reversible thrombocytopenia

Adverse Reactions in Pediatric Patients In pooled pediatric studies, adverse reactions reported in pedia ric patients aking tinidazole were sim lar in nature and frequency to adult findings including nausea, vomiting, diarrhea, taste change, anorexia, and abdominal pain

Bacterial vaginosis The most common adverse reactions in treated patients (incidence >2%), which were not ident fied in the trichomoniasis, giardiasis and amebiasis studies, are gastrointestinal decreased appeti e, and flatulence; renal urinary tract infection, painful urination, and urine abnormality; and other reactions including pelvic pain, vulvo vaginal discomfort, vaginal odor, menorrhagia, and upper respiratory tract infection *[See C inical Studies (14 5)]*

6.2 Postmarketing Experience

The fo lowing adverse reactions have been identified and reported during post approval use of Tinidazole Tablets Because the repor s of these reac ions are volun ary and the population is of uncertain size, it is not always possible to reliably estima e the frequency of the reaction or establish a causal rela ionship to drug exposure

Severe acute hypersensitivity reactions have been reported on initial or subsequent exposure to tinidazole Hypersensitivity reactions may include urticaria, pruritis, angioedema, Stevens Johnson syndrome and erythema multiforme

7 DRUG INTERACTIONS

Although not specifically ident fied in studies with tinidazole, he following drug interactions were reported for me ronidazole, a chemically related nitroimidazole Therefore, these drug in eractions may occur with tinidazole

7.1 Potential Effects of Tinidazole on Other Drugs

Warfarin and O her Oral Coumarin Anticoagulan s As with metronidazole, tinidazole may enhance the e fect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time The dosage of oral anticoagulants may need to be adjusted during tinidazole co administration and up to 8 days after discontinuation

Alcohols, Disul iram Alcoholic beverages and preparations con aining ethanol or propylene glycol should be avoided during tinidazole therapy and for 3 days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur Psychotic reactions have been reported in alcoholic patients using metronidazole and disu firam concurrently Though no sim lar reactions have been reported with tinidazole, tinidazole should not be given o patients who have taken disu firam within he last two weeks

Li hium Me ronidazole has been reported to eleva e serum lithium levels It is not known f tinidazole shares this proper y with metronidazole, but consideration should be given o measuring serum ithium and creatinine levels af er several days of simul aneous lithium and tinidazole treatment to detect poten ial lithium intoxication

Pheny oin, Fosphenytoin Concomitant adminis ration of oral metronidazole and intravenous phenytoin was repor ed to result in prolongation of the half life and reduction in the clearance of phenytoin Me ronidazole did not significantly affect he pharmacokinetics of orally administered phenytoin

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

Fluorouracil Me ronidazole was shown o decrease the clearance of fluorouracil, resulting in an increase in side effec s wi hout an increase in therapeutic benefits If the concomitant use of tinidazole and fluorourac l cannot be avoided, the patient should be monitored for luorouracil associated toxicities

7.2 Potential Effects of Other Drugs on Tinidazole

CYP3A4 Inducers and Inh bitors Simultaneous adminis ration of tinidazole with drugs that induce liver microsomal enzymes, i e , CYP3A4 inducers such as phenobarbi al, r fampin, phenytoin, and fosphenytoin (a pro drug of phenytoin), may accelerate the elimina ion of tinidazole, decreasing the plasma level of inidazole Simultaneous administra ion of drugs that inh bit the activity of iver microsomal enzymes, i e , CYP3A4 inhibitors such as *cime idine and ketoconazole*, may prolong the half life and decrease the plasma clearance of tinidazole, increasing the plasma concen rations of tinidazole

Cholestyramine Cholestyramine was shown o decrease the oral bioava labi ity of metronidazole by 21% Thus, it is advisable to separate dosing of cholestyramine and tinidazole to minimize any potential effect on the oral bioavailab lity of inidazole

Oxytetracycline Oxytetracyc ine was reported to antagonize the therapeutic effect of metronidazole

7.3 Laboratory Test Interactions

Tinidazole, like metronidazole, may interfere with certain ypes 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 A l of the assays in which interference has been repor ed involve enzymatic coup ing of the assay to oxida ion reduction of nicotinamide adenine dinucleotide (NAD⁺↔ NADH) Potential interference is due to the sim larity of absorbance peaks of NADH and inidazole

Tinidazole, ike me ronidazole, may produce transient leukopenia and neutropenia; however, no persistent hematological abnorma ities attributable to inidazole have been observed in clinical studies Total and differen ial leukocyte counts are recommended f re treatment is necessary

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C

The use of tinidazole in pregnant patien s has not been s udied Since tinidazole crosses the placental barrier and enters fe al circulation it should not be adminis ered to pregnant patients in the first trimester

Embryo fetal developmental oxicity studies in pregnant mice indicated no embryo fetal oxicity or ma formations at the highest dose level of 2,500 mg/kg (approxima ely 6 3 fold the highest human herapeutic dose based upon body surface area conversions) In a study with pregnant ra s 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 biologica ly relevant neonatal developmental e fects were observed in rat neonates following maternal doses as high as 600 mg/kg (3 fold the highest human herapeutic dose based upon body surface area conversions) Although there is some evidence of mutagenic potential and animal reproduction studies are not always predictive of human response, the use of tinidazole *af er* the irst trimester of pregnancy requires hat the potential benefi s of the drug be weighed against the possible risks to both the mother and the fetus

8.3 Nursing Mothers

Tinidazole is excreted in breast m lk in concentra ions 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 3 days following the last dose

8.4 Pediatric Use

Other han for use in the treatment of giardiasis and amebiasis in pediatric patien s older han three years of age, safety and effec iveness of tinidazole in pediatric patients have not been established

Pediatric Administration For those unable to swallow tablets, Tinidazole Tablets may be crushed in artificial cherry syrup, o be taken with food *[see Dosage and Administration (2 2)]*

8.5 Geriatric Use

C inical studies of tinidazole did not include sufficient numbers of subjec s aged 65 and over o determine whe her they respond di ferently from younger subjects In general, dose selec ion 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 herapy

8.6 Renal Impairment

Because the pharmacokinetics of tinidazole in pa ients with severe renal impairment (CrCL < 22 mL/min) are not signi icantly di ferent from those in heal hy subjects, no dose adjustments are necessary in these patients

Patients undergoing hemodialysis If tinidazole is administered on the same day as and prior o hemodialysis, it is recommended that an addi ional dose of tinidazole equivalent to one half of the recommended dose be administered after the end of the hemodialysis *[see Clinical Pharmacology (12 3)]*

8.7 Hepatic Impairment

There are no data on inidazole pharmacokine ics in patients wi h impaired hepatic function Reduced elimination of metronidazole, a chemically related ni roimidazole, has been repor ed in this popula ion Usual recommended doses of inidazole should be adminis ered cautiously in patients with hepa ic dysfunction *[see Clinical Pharmacology (12 3)]*

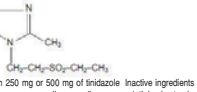
10 OVERDOSAGE

There are no repor ed overdoses with tinidazole in humans ti l date

Trea ment of Overdosage There is no specific an idote for the trea ment of overdosage with inidazole; therefore, trea ment should be symp omatic and supportive Gastric lavage may be helpful Hemodialysis can be considered because approximately 43% of the amount present in the body is e imina ed during a 6 hour hemodialysis session

11 DESCRIPTION

Tinidazole is a syn hetic antipro ozoal and antibacterial agent It is 1 [2 (e hylsulfony]ethyl] 2 methyl 5 nitroimidazole, a second generation 2 methyl 5 nitroimidazole, which has the following chemical structure



Tinidazole pink oral tablets contain 250 mg or 500 mg of tinidazole Inactive ingredients include microcrysta line cellulose, croscarmellose sodium, pregelatinized starch, magnesium stearate, hypromellose, ti anium dioxide, polyethylene glycol, triacetin, FD&C Red 40, FD&C Yellow 6

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tinidazole is an antiprotozoal, ant bacterial agent [See C inical Pharmacology (12 4)]

12.3 Pharmacokinetics

Absorption After oral administration, tinidazole is rapidly and comple ely absorbed A bioavailabi ity study of Tinidazole Tablets was conducted in adult healthy volunteers All subjects received a single oral dose of 2 g (four 500 mg tablets) of Tinidazole Tablets following an overnight fast Oral adminis ration of four 500 mg tablets of Tinidazole Tablets 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 he plasma concentration time curve (AUC, 0 ∞) of 901 6 (± 126 5)µg hr/mL at 72 hours The elimination ha f l fe ($T_{1/2}$) was 13 2 (±1 4) hours Mean plasma levels decreased o 14 3 µg/mL at 24 hours, 3 8 µg/mL at 48 hours and 0 8 µg/mL at 72 hours following adminis ration Steady state condi ions are reached in 2½ 3 days of multi day dosing

Administration of Tinidazole Tablets with food resulted in a delay in T_{max} of approximately 2 hours and a dec ine in Cmax of approximately 10%, compared to fas ed conditions However, administration of Tinidazole Tablets with food did not affect AUC or $T_{1/2}$ in this study In heal hy volunteers, administration of crushed Tinidazole Tablets in art ficial cherry syrup, [prepared as descr bed in *Dosage and Administra ion* (2 2)] af er an overnight fast had no effect on any pharmacokinetic parameter as compared to tablets swallowed whole under fas ed conditions

Distr bution Tinidazole is dis ributed into vir ua ly a l issues and body fluids and also crosses he blood brain barrier The apparent volume of distribution is about 50 liters Plasma pro ein binding of tinidazole is 12% Tinidazole crosses the placental barrier and is secre ed in breast mi k

Metabo ism Tinidazole is significantly metabo ized in humans prior to excretion Tinidazole is partly me abolized by oxidation, hydroxylation, and conjugation Tinidazole is the major drug rela ed consti uent in plasma af er human treatment, along with a sma l amount of he 2 hydroxymethyl metaboli e

Tinidazole is biotransformed mainly by CYP3A4 In an *in vitro* metabo ic drug interac ion study, tinidazole concen rations of up to 75 µg/mL did not inh bit the enzyme ac ivities of CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4

The po ential of tinidazole to induce the metabolism of other drugs has not been evaluated

E imination The plasma half ife 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 adminis ered dose) Approximately 12 % of the drug is excreted in the feces

Patients with impaired renal function The pharmacokinetics of tinidazole in patients with severe renal impairment (CrCL < 22 mL/min) are not sign fican ly d fferent from the pharmacokinetics seen in healthy subjects However, during hemodialysis, clearance of inidazole is signi icantly increased; the half ife is reduced from 12 0 hours to 4 9 hours Approximately 43% of he amount present in the body is eliminated during a 6 hour hemodialysis session *[see Use in Spec fic Populations (8 6)]* The pharmacokinetics of inidazole in patien s undergoing routine continuous peritoneal dialysis have not been inves igated

Patients with impaired hepatic function There are no data on tinidazole pharmacokinetics in patients with impaired hepatic function Reduction of metabo ic e imination of metronidazole, a chemically related nitroimidazole, in patients with hepa ic dysfunction has been reported in several studies *[see Use in Specific Popula ions (8 7)]*

12.4 Microbiology

Mechanism of Action Tinidazole is an antiprotozoal, ant bacterial agent The nitro group of inidazole is reduced by cell extrac s of *Trichomonas* The free nitro radical generated as a result of this reduction may be respons ble for the antiprotozoal activity

Chemically reduced inidazole was shown o release nitrites and cause damage to puri ied bacterial DNA *in vitro*

Addi ionally, the drug caused DNA base changes in bacterial cells and DNA s rand breakage in mammalian ce ls The mechanism by which tinidazole exhibits activity against *Giardia and Entamoeba species* is not known

Antibac erial Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis *[see Indications and Usage (1 4)]*; standard methodology for the susceptibility testing of poten ial bac erial pathogens, *Gardnerella vaginalis*, *Mob luncus spp* or *Mycoplasma hominis*, has not been de ined The following in vitro data are available, but heir c inical significance is unknown Tinidazole is active in vitro against most strains of the following organisms that have been reported to be associated with bacterial vaginosis

Bacteroides spp
Gardnerella vaginalis
Prevotella spp

Tinidazole does not appear to have activity against most strains of vaginal lac obaci li

Antiprotozoal Tinidazole demonstrates ac ivity bo h in vitro and in clinical infections against he following protozoa *Trichomonas vaginalis*; *Giardia duodena is* (also termed *G lamb lia*); and *Entamoeba his olytica*

For protozoal parasites, standardized susceptibi ity tests do not exist for use in clinical microbiology laboratories

Drug Resistance The development of resistance to inidazole by *G duodenalis*, *E histolytica*, or bacteria associated with bac erial vaginosis has not been examined

Cross resistance Approximately 38% of *T vaginalis* isolates exhibiting reduced suscept bi ity o metronidazole also show reduced suscep ib ity to tinidazole *in vitro* The clinical significance of such an effect is not known

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fert ility

Metronidazole, a chemically related nitroimidazole, has been repor ed to be carcinogenic in mice and rats but not hamsters In several s udies metronidazole showed evidence of pulmonary, hepatic, and lymphatic tumorigenesis in mice and mammary and hepa ic tumors in female rats Tinidazole carcinogenicity studies in rats, mice or hamsters have not been repor ed

Tinidazole was mutagenic in the TA 100, *S typhimurium* tester strain both with and without he metabolic activation system and was negative for mutagenicity in he 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 s rain of *Klebsiella pneumonia* Tinidazole was negative for mutagenicity in a mammalian ce l culture system uti izing Chinese hamster lung V79 cells (HGPRT test sys em) and negative for genotoxicity in the Chinese hamster ovary (CHO) sister chromatid exchange assay Tinidazole was positive for *in vivo* genotoxicity in he mouse micronucleus assay

In a 60 day fert lity study, tinidazole reduced fert li y and produced testicular histopathology in male rats at a 600 mg/kg/day dose level (approximately 3 fold the highest human herapeutic dose based upon body surface area conversions) Spermatogenic effects resulted from 300 and 600 mg/kg/day dose levels The no observed adverse reaction level for es icular and sperma ogenic effects was 100 mg kg/day (approxima ely 0 5 fold the highest human herapeutic dose based upon body surface area conversions) This e fect is charac eristic of agents in the 5 nitroimidazole class

13.2 Animal Toxicology and/or Pharmacology

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 in raperitoneal administra ion In ra s, the LD_{50} was > 2,000 mg/kg for both oral and intraperitoneal administration

A repeated dose toxicology study has been performed in beagle dogs using oral dosing of inidazole at 100 mg/kg/day, 300 mg kg/day, and 1000 mg kg/day for 28 days On Day 18 of he study, the highest dose was lowered to 600 mg/kg/day due to severe c inical symptoms The two compound related effec s observed in the dogs treated wi h tinidazole were increased atrophy of the thymus in bo h sexes at he middle and high doses, and atrophy of he prostate at all doses in the males A no adverse effect level (NOAEL) of 100 mg/kg/day for females was determined There was no NOAEL ident fied for males because of minimal atrophy of the prostate at 100 mg/kg/day (approximately 0 9 fold the highest human dose based upon plasma AUC comparisons)

14 CLINICAL STUDIES

14.1 Trichomoniasis

Tinidazole (2 g single oral dose) use in trichomoniasis has been we l documented in 34 pub ished reports from the world literature involving over 2,800 patients treated with inidazole 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 mon h, repor ed cure ra es ranged from 92% (37/40) o 100% (65/65) (n=172 total subjects) In four published, blinded, randomized, comparative studies where ef icacy was assessed by wet mount be ween 7 14 days post treatment, reported cure rates ranged from 80% (8/10) to 100% (16/16) (n=116 total subjects) In hese s udies, inidazole was superior o placebo and comparable to other anti trichomonal drugs The single oral 2 g inidazole 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 reatment and reported cure rates ranged from 83% (25/30) to 100% (80/80) (n=142 total subjects)

14.2 Giardiasis

Tinidazole (2 g single dose) use in giardiasis has been documen ed in 19 pub ished reports from the world literature involving over 1,600 patients (adults and pediatric patients) In eight contro led studies involving a total of 619 subjec s of whom 299 were given the 2 g × 1 day (50 mg/kg × 1 day in pediatric patients) oral dose of tinidazole, reported cure ra es ranged from 80% (40/50) to 100% (15/15) In three of these rials where the compara or 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

14.3 Intestinal Amebiasis

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

14.4 Amebic Liver Abscess

Tinidazole use in amebic liver abscess has been documented in 18 pub ished reports from he world litera ure involving over 470 patients Most reports u ilized tinidazole 2 g/day × 2 5 days In seven pub ished, randomized, controlled studies (1 double blind, 1 single blind, 5 open labe) of the 2 g/day × 2 5 days oral dose of tinidazole accompanied by aspiration of the iver abscess when clinica ly necessary, reported cure rates among 133 subjects ranged from 81% (17/21) to 100% (16/16) Four of hese studies ut ized at least 3 days of tinidazole

14.5 Bacterial Vaginosis

A randomized, double blind, placebo controlled c inical trial in 235 non pregnant women was conducted to evalua e the ef icacy of tinidazole for the treatment of bacterial vaginosis A clinical diagnosis of bacterial vaginosis was based on Amsel's criteria and de ined by the presence of an abnormal homogeneous vaginal discharge that (a) has a pH of greater han 4 5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution, and (c) contains ≥ 20% clue cells on microscopic examina ion Clinical cure required a return to normal vaginal discharge and resolu ion of a l Amsel's criteria A microbiologic diagnosis of bacterial vaginosis was based on Gram s ain of the vaginal smear demonstrating (a) markedly reduced or absent *Lac obaci lus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells, with quant fication of these bac erial morphotypes o de ermine the Nugent score, where a score ≥4 was required for study inclusion and a score of 0 3 considered a microbiologic cure Therapeu ic cure was a composite endpoint, consisting of both a clinical cure and microbiologic cure In patien s with all four Amsel's criteria and with a baseline Nugent score ≥4, inidazole oral ablets given as either 2 g once da ly for 2 days or 1 g once da ly for 5 days demonstrated superior efficacy over placebo tablets as measured by herapeutic cure, clinical cure, and a microbiologic cure

Table 2 Efficacy of Tinidazole Tablets in the Treatment of Bacterial Vaginosis in a Randomized, Double B ind, Double Dummy, Placebo Controlled Trial: Modified Intent to Treat Population[1] (n=227)

Outcome	Tinidazole Tablets 1 g × 5 days (n=76)	Tinidazole Tablets 2g x 2 days (n=73)	Placebo (n=78)
	%Cure	%Cure	%Cure
Therapeutic Cure	36 8	27 4	5 1
Difference[2]	31 7	22 3	
97 5%CI[3]	(16 8,46 6)	(8 0, 36 6)	
Clinical Cure	51 3	35 6	11 5
Difference[2]	39 8	24 1	
97 5%CI[3]	(23 3, 56 3)	(7 8, 40 3)	
Nugent Score Cure	38 2	27 4	
Difference[2]	33 1	22 3	
97 5%CI[3]	(18 1, 48 0)	(8 0, 36 6)	

[1]Modi ied Intent to Treat de ined as a l patients randomized with a baseline Nugent score of at least 4

[2]Difference in cure rates (Tinidazole Table s placebo)

[3]CI confidence in erval

p values for both Tinidazole regimens vs placebo for therapeu ic, c inical and Nugent score cure rates for both 2 and 5 days <0 001

The therapeutic cure ra es repor ed in this clinical study conducted with Tinidazole were based on resolution of 4 out of 4 Amsel's criteria and a Nugent score of <4 The cure rates for previous c inical studies with o her products approved for bac erial vaginosis were based on resolution of either 2 or 3 out of 4 Amsel's criteria At he time of approval for other products for bacterial vaginosis, there was no requirement for a Nugent score on Gram stain, resulting in higher reported rates of cure for bacterial vaginosis for those products than for those reported here for tinidazole

16 HOW SUPPLIED/STORAGE AND HANDLING

Tinidazole Tablets 250 mg are pink, circular, film coated scored tablets, with T | P debossed on one side and 250 on the o her, supplied in bo tles with ch ld resistant caps as

NDC 67668 181 40 Bot le of 40

Tinidazole Tablets 500 mg are pink, capsule shaped, f lm coated scored table s, with T | P debossed on one side and 500 on the other, supp ied in bottles with child resistant caps as

NDC 67668 182 60 Bot le of 60

NDC 67668 182 20 Bot le of 20

Storage Store at controlled room temperature 20 25° C (68 77° F); excursions permitted o 15 30° C (59 86° F) [see USP] Protect con en s from light

17 PATIENT COUNSELING INFORMATION

17.1 Administration of Drug

Patients should be told to take Tinidazole Tablets wi h food to minimize he incidence of epigastric discomfort and other gastrointestinal side e fects Food does not affect the oral bioavailab li y of tinidazole

17.2 Alcohol Avoidance

Patients should be told to avoid alcoholic beverages and prepara ions containing e hanol or propylene glycol during Tinidazole Tablets therapy and for 3 days afterward because abdominal cramps, nausea, vomiting, headaches, and lushing may occur

17.3 Drug Resistance

Patients should be counseled that antibacterial drugs including Tinidazole Tablets should only be used to reat bacterial infections They do not treat viral infections (e g , the common cold) When Tinidazole Tablets are prescribed o reat a bacterial infection, patien s should be told that although it is common to feel better early in the course of therapy, he medication should be aken exactly as directed Skipping doses or not completing the full course of therapy may (1) decrease the effec iveness of the immediate reatment and (2) increase the like lihood that bacteria will develop resistance and wi l not be trea able by Tinidazole Tablets or other ant bacterial drugs in the future

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